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Patentanmeldung Nr. **Patent application No.** **Demande de brevet n°**

03290951.7

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Chemical compounds

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CHEMICAL COMPOUNDS

The present invention relates to quinazoline derivatives for use in the treatment of disease in particular proliferative diseases such as cancer and in the preparation of medicaments for use in the treatment of proliferative diseases, and to processes for their preparation, as well as pharmaceutical compositions containing them as active ingredient.

Cancer (and other hyperproliferative diseases) are characterised by uncontrolled cellular proliferation. This loss of the normal regulation of cell proliferation often appears to occur as the result of genetic damage to cellular pathways that control progress through the cell cycle.

In eukaryotes, an ordered cascade of protein phosphorylation is thought to control the cell cycle. Several families of protein kinases that play critical roles in this cascade have now been identified. The activity of many of these kinases is increased in human tumours when compared to normal tissue. This can occur by either increased levels of expression of the protein (as a result of gene amplification for example), or by changes in expression of co activators or inhibitory proteins.

The first identified, and most widely studied of these cell cycle regulators have been the cyclin dependent kinases (or CDKs). Activity of specific CDKs at specific times is essential for both initiation and coordinated progress through the cell cycle. For example, the CDK4 protein appears to control entry into the cell cycle (the G0-G1-S transition) by phosphorylating the retinoblastoma gene product pRb. This stimulates the release of the transcription factor E2F from pRb, which then acts to increase the transcription of genes necessary for entry into S phase. The catalytic activity of CDK4 is stimulated by binding to a partner protein, Cyclin D. One of the first demonstrations of a direct link between cancer and the cell cycle was made with the observation that the Cyclin D1 gene was amplified and cyclin D protein levels increased (and hence the activity of CDK4 increased) in many human tumours (Reviewed in Sherr, 1996, Science 274: 1672-1677; Pines, 1995, Seminars in Cancer Biology 6: 63-72). Other studies (Loda et al., 1997, Nature Medicine 3(2): 231-234; Gemma et al., 1996, International Journal of Cancer 68(5): 605-11; Elledge et al. 1996, Trends in Cell Biology 6; 388-392) have shown that negative regulators of CDK function are frequently down regulated or deleted in human tumours again leading to inappropriate activation of these kinases.

More recently, protein kinases that are structurally distinct from the CDK family have been identified which play critical roles in regulating the cell cycle and which also appear to be important in oncogenesis. These include the newly identified human homologues of the *Drosophila* aurora and *S.cerevisiae* Ipl1 proteins. The three human homologues of these genes Aurora-A, Aurora-B and Aurora-C (also known as aurora2, aurora1 and aurora3 respectively) encode cell cycle regulated serine-threonine protein kinases (summarised in Adams *et al.*, 2001, Trends in Cell Biology. 11(2): 49-54). These show a peak of expression and kinase activity through G2 and mitosis. Several observations implicate the involvement of human aurora proteins in cancer. This evidence is particularly strong for Aurora-A. The Aurora-A gene maps to chromosome 20q13, a region that is frequently amplified in human tumours including both breast and colon tumours. Aurora-A may be the major target gene of this amplicon, since Aurora-A DNA is amplified and mRNA overexpressed in greater than 50% of primary human colorectal cancers. In these tumours Aurora-A protein levels appear greatly elevated compared to adjacent normal tissue. In addition, transfection of rodent fibroblasts with human Aurora-A leads to transformation, conferring the ability to grow in soft agar and form tumours in nude mice (Bischoff et al., 1998, The EMBO Journal. 17(11): 3052-3065). Other work (Zhou et al., 1998, Nature Genetics. 20(2): 189-93) has shown that artificial overexpression of Aurora-A leads to an increase in centrosome number and an increase in aneuploidy, a known event in the development of cancer. Other work has shown an increase in expression of Aurora-B (Adams *et al.*, 2001, Chromsoma. 110(2):65-74) and Aurora-C (Kimura *et al.*, 1999, Journal of Biological Chemistry, 274(11): 7334-40) in tumour cells when compared to normal cells.

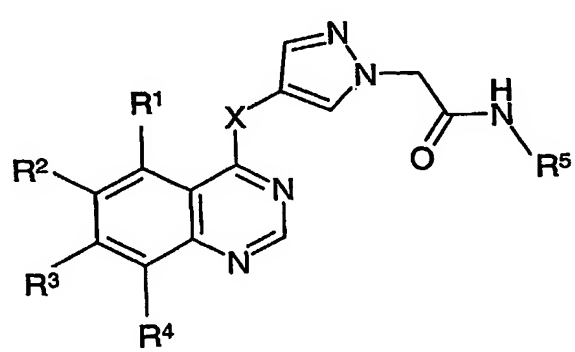
Importantly, it has also been demonstrated that abrogation of Aurora-A expression and function by antisense oligonucleotide treatment of human tumour cell lines (WO 97/22702 and WO 99/37788) leads to cell cycle arrest and exerts an antiproliferative effect in these tumour cell lines. Additionally, small molecule inhibitors of Aurora-A and Aurora-B have been demonstrated to have an antiproliferative effect in human tumour cells (Keen *et al.* 2001, Poster #2455, American Association of Cancer research annual meeting). This indicates that inhibition of the function of Aurora-A and/or Aurora-B will have an antiproliferative effect that may be useful in the treatment of human tumours and other hyperproliferative diseases. Further, inhibition of Aurora kinases as a therapeutic approach to these diseases may have significant advantages over targeting signalling pathways upstream of the cell cycle (e.g. those activated by growth factor receptor tyrosine kinases such as epidermal growth factor receptor

(EGFR) or other receptors). Since the cell cycle is ultimately downstream of all of these diverse signalling events, cell cycle directed therapies such as inhibition of Aurora kinases would be predicted to be active across all proliferating tumour cells, whilst approaches directed at specific signalling molecules (e.g. EGFR) would be predicted to be active only in the subset of tumour cells which express those receptors. It is also believed that significant "cross talk" exists between these signalling pathways meaning that inhibition of one component may be compensated for by another.

A number of quinazoline derivatives have been proposed hitherto for use in the inhibition of Aurora kinases. For example, WO 01/21594, WO 01/21595 and WO 01/215968 describe the use of certain phenyl-quinazoline compounds as Aurora-A kinase inhibitors, which may be useful in the treatment of proliferative diseases and WO 01/21597 discloses other quinazoline derivatives as inhibitors of Aurora-A kinase. Additionally, WO 02/00649 discloses quinazoline derivative bearing a 5-membered heteroaromatic ring where the ring is, in particular, substituted thiazole or substituted thiophene. However despite the compounds of WO 02/00649 there still exists a need for further compounds having Aurora kinase inhibitory properties.

The applicants have been successful in finding a novel series of compounds which inhibit the effects of the Aurora kinases and in particular Aurora-A kinase and/or Aurora-B kinase which are thus of use in the treatment of proliferative diseases such as cancer, in particular in such diseases such as colorectal, breast or pancreatic cancer where Aurora kinases are known to be active.

According to one aspect of the present invention there is provided a compound of formula (I)



formula (I)

or a salt, ester or prodrug thereof;

where:

X is O or NR^6;

$\mathbf{R^6}$ is hydrogen or C_{1-4}alkyl;

$\mathbf{R^1}$ is hydrogen, halo, or $-X^1R^{11}$;

$\mathbf{X^1}$ is a direct bond, -O-, -NH- or $-N(C_{1-6}$alkyl)-;

$\mathbf{R^{11}}$ is hydrogen, heterocyclyl or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is optionally substituted by heterocyclyl, halo, hydroxy, C_{1-4}alkoxy or $-NR^9R^{10}$;

$\mathbf{R^2}$ is hydrogen, halo, nitro, cyano or $-X^2R^{12}$;

$\mathbf{X^2}$ is a direct bond, -O-, -NH- or $-N(C_{1-6}$alkyl)-;

$\mathbf{R^{12}}$ is hydrogen, heterocyclyl or a group selected from aryl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is optionally substituted by aryl, heterocyclyl, halo, hydroxy or $-NR^{15}R^{16}$;

$\mathbf{R^3}$ is hydrogen, halo or $-X^3R^{13}$;

$\mathbf{X^3}$ is a direct bond, $-CH_2=CH_2-$, -O-, -NH- or $-N(C_{1-6}$alkyl)-;

$\mathbf{R^{13}}$ is hydrogen, heterocyclyl or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is optionally substituted by $-NR^7R^8$, heterocyclyl, halo, hydroxy or C_{1-4}alkoxy;

$\mathbf{R^7}$ and $\mathbf{R^8}$ are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, hydroxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, hydroxyC_{3-6}cycloalkylC_{1-3}alkyl, C_{1-3}alkoxyC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{3-6}cycloalkylC_{1-3}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-3}alkylaminoC_{1-6}alkyl and di(C_{1-3}alkyl)aminoC_{1-6}alkyl;

or $\mathbf{R^7}$ and $\mathbf{R^8}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is optionally substituted on carbon or nitrogen by 1 or 2 groups independently selected from C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkoxyC_{1-4}alkoxy, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$;

$\mathbf{R^4}$ is selected from hydrogen, halo or $-X^4R^{14}$;

$\mathbf{X^4}$ is a direct bond, -O-, -NH- or $-N(C_{1-6}$alkyl)-;

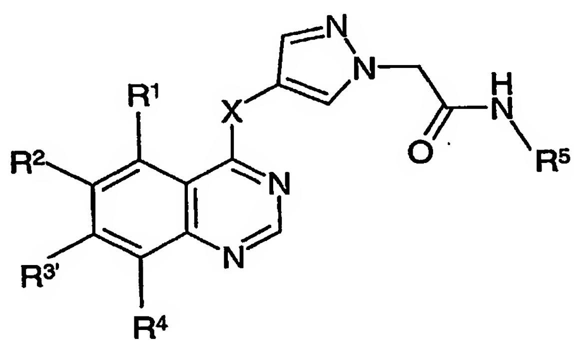
R^{14} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl;

R^5 is aryl or heteroaryl optionally substituted by 1, 2 or 3 substituents independently selected from halo, hydroxy, cyano, nitro, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, CONHR^{17}, NHCOR^{18} and S(O)$_p$R^{19} where p is 0, 1 or 2;

R^9, R^{10}, R^{15} and **R^{16}** are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl and di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

R^{17}, R^{18} and **R^{19}** are independently selected from hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkenyl and C_{2-4}alkynyl.

In a further aspect the present invention provides a compound of formula (IA)



formula (IA)

where X, R^1, R^2, R^4 and R^5 are as defined in relation to formula (I) and

R$^{3'}$ is hydrogen, halo or $-X^{3'}R^{13'}$;

$X^{3'}$ is a direct bond, $-CH_2=CH_2-$, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$R^{13'}$ is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is substituted by $-NR^{7'}R^{8'}$;

$R^{7'}$ and **$R^{8'}$** are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, phosphonooxyC_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, phosphonooxyC_{3-6}cycloalkyl, phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl, phosphonooxyC_{3-6}cycloalkylC_{1-3}alkyl, C_{1-3}alkoxyC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{3-6}cycloalkylC_{1-3}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-3}alkylaminoC_{1-6}alkyl and di(C_{1-3}alkyl)aminoC_{1-6}alkyl; provided that at least one of R$^{7'}$ and R$^{8'}$ contains a phosphonooxy substituent;

or **$R^{7'}$** and **$R^{8'}$** together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is

optionally selected from N, NH, O, S, SO and SO_2, and which ring is substituted on carbon or nitrogen by 1 or 2 groups independently selected from phosphonooxy, phoshonooxyC_{1-4}alkyl and phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, and where a ring -CH_2- is optionally replaced with a –C(O)-.

In this specification the term alkyl when used either alone or as a suffix or prefix includes straight-chain and branched-chain saturated structures comprising carbon and hydrogen atoms. References to individual alkyl groups such as propyl are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as *tert*-butyl are specific for the branched chain version only. An analogous convention applies to other generic terms such as alkenyl and alkynyl.

Cycloalkyl is a monocyclic alkyl group, and cycloalkenyl and cycloalkynyl are monocyclic alkenyl and alkynyl groups respectively.

The prefix C_{m-n} in C_{m-n}alkyl and other terms (where m and n are integers) indicates the range of carbon atoms that are present in the group, for example C_{1-3}alkyl includes C_1alkyl (methyl), C_2alkyl (ethyl) and C_3alkyl (propyl or isopropyl).

The terms C_{m-n}alkoxy comprise –O-C_{m-n}alkyl groups.

The term halo includes fluoro, chloro, bromo and iodo.

Aryl groups may be monocyclic or bicyclic.

Unless otherwise stated heteroaryl groups are monocyclic or bicyclic aromatic rings containing 5 to 10 ring atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen where a ring nitrogen or sulphur may be oxidised.

Heterocyclyl is a saturated, partially saturated or unsaturated, monocyclic or bicyclic ring containing 4 to 7 ring atoms of which 1, 2 or 3 ring atoms selected from nitrogen, sulphur or oxygen, which may be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)-; wherein a ring nitrogen or sulphur atom is optionally oxidised to form the N-oxide or S-oxide(s); wherein a ring –NH is optionally substituted by acetyl, formyl, methyl or mesyl; and wherein a ring is optionally substituted by 1 or 2 groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxy and haloC_{1-4}alkyl. When heterocyclyl is used within the definition of R^3, in one aspect of the invention it is a saturated monocyclic ring containing 4 to 7 ring atoms of which 1 or 2 are nitrogen and where the ring is optionally substituted by C_{1-4}alkyl, hydroxyC_{1-4}alkyl and hydroxy.

Phosphonooxy is in one aspect a group of formula $-OP(O)(OH)_2$. However the term phosphonooxy also includes salts such as those formed with alkali metal ions such as sodium or potassium ions or alkaline earth metal ions, for example calcium or magnesium ions.

This specification also makes use of several composite terms to describe groups comprising more than one functionality. Such terms are to be interpreted as is understood in the art. For example C_{m-n}cycloalkylC_{m-n}alkyl comprises C_{m-n}alkyl substituted by C_{m-n}cycloalkyl.

HaloC_{m-n}alkyl is a C_{m-n}alkyl group that is substituted by 1, 2 or 3 halo substituents. Similarly, haloC_{m-n}cycloalkyl and haloC_{m-n}cycloalkylC_{m-n}alkyl groups may contain 1, 2 or 3 halo substituents.

HydroxyC_{m-n}alkyl is a C_{m-n}alkyl group that is substituted by 1, 2 or 3 hydroxy substituents. Similarly, hydroxyC_{m-n}cycloalkyl and hydroxyC_{m-n}cycloalkylC_{m-n}alkyl groups may contain 1, 2 or 3 hydroxy substituents.

C_{m-n}alkoxyC_{m-n}alkyl is a C_{m-n}alkyl group that is substituted by 1, 2 or 3 C_{m-n}alkoxy substituents. Similarly, C_{m-n}alkoxyC_{m-n}cycloalkyl and C_{m-n}alkoxyC_{m-n}cycloalkylC_{m-n}alkyl groups may contain 1, 2 or 3 C_{m-n}alkoxy substituents.

Where optional substituents are chosen from 1 or 2 or from 1, 2, or 3 groups or substituents it is to be understood that this definition includes all substituents being chosen from one of the specified groups i.e. all substituents being the same or the substituents being chosen from two or more of the specified groups i.e. the substituents not being the same.

Unless specifically stated the bonding atom of a group may be any atom of that group so for example propyl includes prop-1-yl and prop-2-yl.

Compounds of the present invention have been named with the aid of computer software (ACD/Name version 6.6 or ACD Name Batch version 6.0).

Suitable values for any R group or any part or substituent for such groups include:

for C_{1-4}alkyl:	methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tert-butyl;
for C_{1-6}alkyl:	C_{1-4}alkyl, pentyl, neopentyl, dimethylbutyl and hexyl;
for C_{2-4}alkenyl:	vinyl, allyl and but-2-enyl;
for C_{2-6}alkenyl:	C_{2-4}alkenyl, 3-methylbut-2-enyl and 3-methylpent-2-enyl;
for C_{2-4}alkynyl:	ethynyl, propargyl and prop-1-ynyl;
for C_{2-6}alkynyl:	C_{2-4}alkynyl, pent-4-ynyl and 2-methylpent-4-ynyl;
for C_{3-6}cycloalkyl:	cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

for C_{3-6}cycloalkenyl: cyclobutenyl, cyclopentenyl, cyclohexenyl and cyclohex-1,4-dienyl;

for C_{3-6}cycloalkylC_{1-3}alkyl: cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylethyl and cyclobutylethyl;

for C_{1-4}alkoxy: methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy;

for C_{1-3}alkoxyC_{1-4}alkyl: methoxymethyl, methoxyethyl, methoxypropyl and ethoxyethyl;

for C_{1-3}alkoxyC_{1-6}alkyl: C_{1-3}alkoxyC_{1-4}alkyl, methoxybutyl and ethoxybutyl;

for C_{1-3}alkoxyC_{3-6}cycloalkyl: methoxycyclobutyl, methoxycyclopentyl and ethoxycyclopentyl;

for C_{1-3}alkoxyC_{3-6}cycloalkylC_{1-3}alkyl: methoxycyclobutylmethyl and methoxycyclopentylmethyl;

for C_{1-4}alkoxyC_{1-4}alkoxy: methoxymethoxy, methoxyethoxy and ethoxyethoxy;

for hydroxyC_{1-4}alkyl: hydroxymethyl, 2-hydroxyethoxy and 3-hydroxypropoxy;

for hydroxyC_{1-6}alkyl: hydroxyC_{1-4}alkyl, 3-hydroxypentyl and 6-hydroxyhexyl;

for hydroxyC_{3-6}cycloalkyl: 2-hydroxycyclopropyl, 2-hydroxycyclobutyl and 2-hydroxycyclopentyl;

for hydroxyC_{3-6}cycloalkylC_{1-3}alkyl: 2-hydroxycyclopropylmethyl and 2-hydroxycyclobutylmethyl;

for hydroxyC_{1-4}alkylC_{3-6}cycloalkyl: 1-(hydroxymethyl)cyclopentyl;

for hydroxyC_{1-4}alkoxyC_{1-4}alkyl: 2-(2-hydroxyethyl)ethyl;

for haloC_{1-6}alkyl: chloromethyl, trifluoromethyl and 3,3,3-trifluoropropyl;

for haloC_{3-6}cycloalkyl: 2-chlorocyclopropyl and 2-chlorocyclobutyl;

for haloC_{3-6}cycloalkylC_{1-3}alkyl: 2-chlorocyclopropylmethyl and 2-chlorocyclobutylmethyl;

for cyanoC_{1-4}alkyl: cyanomethyl and 2-cyanoethyl;

for aminoC_{1-6}alkyl: aminomethyl, 2-aminoethyl, 2-aminopropyl and 4-aminobutyl;

for C_{1-3}alkylaminoC_{1-6}alkyl: 2-(methylamino)ethyl and 3-(ethylaminopropyl);

for di(C_{1-3}alkyl)aminoC_{1-6}alkyl: 2-(dimethylamino)ethyl 2-[methyl(ethyl)amino]ethyl and 2-(diethylamino)ethyl;

for C_{1-6}alkylamino: methylamino, ethylamino, propylamino and isopropylamino;

for di(C_{1-6}alkyl)amino: dimethylamine, methyl(ethyl)amino and diethylamino;

for aryl: phenyl and naphthyl

for heteroaryl: furyl, thienyl, pyrrolyl, pyrazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, quinazolinyl and quinolinyl

for heterocyclyl: azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, azepanyl, diazepanyl, pyridyl, imidazolyl, tetrahydrofuranyl, tetrahydropyranyl, furanyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydro-2H-pyranyl and morpholinyl.

for phosphonooxyC_{1-6}alkyl: phosphonooxymethyl and 2-phosphonooxyethyl;

for phosphonooxyC_{3-6}cycloalkylC_{1-3}alkyl: 2-phosphonooxycyclopropylmethyl and 2-phosphonooxycyclobutylmethyl;

for phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl: 1-(phosphonooxymethyl)cyclopentyl;

for phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl: 2-(2-hydroxyethoxy)ethyl.

Within the present invention, it is to be understood that, insofar as certain of compounds of formula (I) or formula (IA) herein defined may exist in optically active or racemic forms by virtue of one or more asymmetric carbon or sulphur atoms, the invention includes in its definition any such optically active or racemic form which possesses aurora kinase inhibitory activity and in particular Aurora-A and/or Aurora-B kinase inhibitory activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Within the present invention it is to be understood that a compound of formula (I) or formula (IA) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has Aurora kinase inhibitory activity and in particular Aurora-A and/or Aurora-B kinase inhibitory activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings.

It is also to be understood that certain compounds of formula (I) or formula (IA) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have Aurora kinase inhibitory activity and in particular Aurora-A and/or Aurora-B kinase inhibitory activity.

The present invention relates to the compounds of formula (I) or formula (IA) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the

production of the compounds of formula (I) or formula (IA) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of compounds of formula (I) or formula (IA) as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include but are not limited to furmarate, methanesulphonate, hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In addition where compounds of formula (I) or formula (IA) are sufficiently acidic, salts are base salts and examples include but are not limited to, an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine, ethanolamine, diethanolamine, triethanolamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, dibenzylamine or amino acids such as lysine.

The compounds of formula (I) or formula (IA) may also be provided as *in vivo* hydrolysable esters. An *in vivo* hydrolysable ester of a compound of formula (I) or formula (II) containing carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol. Such esters can be identified by administering, for example, intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluid.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in-vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups for hydroxy include C_1-$_{10}$alkanoyl, for example formyl, acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C_1-$_{10}$alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-C_1-$_4$alkylcarbamoyl and *N*-(di-C_1-$_4$alkylaminoethyl)-*N*-

C_{1-4}alkylcarbamoyl (to give carbamates); di-C_{1-4}alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, C_{1-4}alkylaminomethyl and di-(C_{1-4}alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting *in vivo* hydrolysable esters include, for example, $R^AC(O)OC_{1-6}$alkyl-CO-, wherein R^A is for example, benzyloxy-C_{1-4}alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-C_{1-4}piperazino-C_{1-4}alkyl, piperazino-C_{1-4}alkyl and morpholino-C_{1-4}alkyl.

Preferred values of X, R^1, R^2, R^3, $R^{3'}$, R^4 and R^5 for compounds of formula (I) and formula (IA) are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one aspect of the invention X is NR^6. In another aspect X is NH.

In one aspect of the invention R^6 is hydrogen or methyl. In another aspect R^6 is hydrogen.

In one aspect of the invention R^1 is hydrogen or $-OR^{11}$. In another aspect R^1 is hydrogen.

In one aspect of the invention X^1 is a direct bond or -O-. In another aspect X^1 is a direct bond.

In one aspect of the invention R^{11} is hydrogen, heterocyclyl selected from piperidinyl or pyrrolidinyl or C_{1-4}alkyl (optionally substituted by hydroxy, C_{1-4}alkoxy, amino, C_{1-4}alkylamino or di(C_{1-4}alkyl)amino). In another aspect R^{11} is hydrogen, C_{1-4}alkyl or C_{1-4}alkoxy. In another aspect R^{11} is hydrogen.

In one aspect of the invention R^2 is hydrogen or $-OR^{12}$. In another aspect R^2 is hydrogen or methoxy. In a further aspect R^2 is hydrogen. In yet a further aspect R^2 is methoxy.

In one aspect of the invention X^2 is a direct bond or -O-.

In one aspect of the invention R^{12} is hydrogen, C_{1-4}alkyl (ptionally substituted by heterocyclyl) or heterocyclyl. In another aspect R^{12} is hydrogen or C_{1-4}alkyl. In another aspect of the invention R^{12} is hydrogen. In a further aspect of the invention R^{12} is methyl.

In one aspect of the invention R^3 is $-X^3R^{13}$. In a further aspect R^3 is selected from 3-chloropropoxy, 3-[2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-[(2-hydroxyethyl)(isobutyl)amino]propoxy, 3-[(2-hydroxyethyl)(propyl)amino]propoxy, 3-

piperidin-1-ylpropoxy, 3-pyrrolidin-1-ylpropoxy, 3-(diethylamino)propoxy, 3-piperazin-1-ylpropoxy, 3-[(2-hydroxyethyl)(methyl)amino]propoxy, 3-(cyclopropylamino)propoxy, 3-{[2-(dimethylamino)ethyl](methyl)amino}propoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 3-[bis(2-hydroxyethyl)amino]propoxy, 3-[ethyl(methyl)amino]propoxy, 3-[ethyl(2-hydroxyethyl)amino]propoxy, 3-{[2-(dimethylamino)ethyl](ethyl)amino}propoxy, 3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy, 3-[(cyclopropylmethyl)amino]propoxy, 3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[methyl(propargyl)amino]propoxy, 3-[allyl(methyl)amino]propoxy, 3-[isobutyl(methyl)amino]propoxy, 3-(3-hydroxypiperidin-1-yl)propoxy, 3-[4-(hydroxymethyl)piperidin-1-yl]propoxy, 3-[methyl(propyl)amino]propoxy, 3-[cyclopropylmethyl(propyl)amino]propoxy, 3-{[2-(diethylamino)ethyl](methyl)amino}propoxy, 3-{[2-(diethylamino)ethyl](ethyl)amino}propoxy, 3-(4-methyl-1,4-diazepan-1-yl)propoxy, 3-[(2-hydroxyethyl)(isopropyl)amino]propoxy, 3-[cyclopropyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy, 3-[cyclobutyl(2-hydroxyethyl)amino]propoxy, 3-[cyclopropylmethyl(2-hydroxyethyl)amino]propoxy, 3-[cyclobutylmethyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxy)propargylamino]propoxy, 3-[allyl(2-hydroxyethyl)amino]propoxy, 3-[(2-hydroxyethyl)neopentylamino]propoxy, 3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy, 3-azetidin-3-ylpropoxy, 3-[cyclopentyl(2-hydroxyethyl)amino]propoxy, 3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy, 3-[(2-cyanoethyl)(2-hydroxyethyl)amino]propoxy and 3-(dimethylamino)propoxy. In another aspect R^3 is selected from 3-[2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 3-[(2-hydroxyethyl)(isobutyl)amino]propoxy, 3-[(2-hydroxyethyl)(propyl)amino]propoxy, 3-[ethyl(2-hydroxyethyl)amino]propoxy, 3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy, 3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy, 3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy, 3-[cyclobutyl(2-hydroxyethyl)amino]propoxy, 3-[cyclopropylmethyl(2-hydroxyethyl)amino]propoxy and 3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy.

In one aspect of the invention X^3 is $-CH_2=CH_2-$, -O- or -NH-. In another aspect X^3 is -O-.

In one aspect of the invention R^{13} is C_{1-6}alkyl substituted by $-NR^7R^8$, heterocyclyl or halo. In a further aspect of the invention R^{13} is ethyl or propyl, both of which are substituted by $-NR^7R^8$, heterocyclyl or halo. In yet a further aspect of the invention R^{13} is propyl substituted by chloro, $-NR^7R^8$ or a heterocyclyl selected from pyrrolidinyl, piperidinyl,

piperazinyl, diazepanyl and azetidinyl where the heterocyclyl is optionally substituted by hydroxy, methyl, hydroxymethyl or 2-hydroxyethyl. In another aspect R^{13} is propyl substituted by chloro or $-NR^7R^8$. In a further aspect R^{13} is propyl substituted by $-NR^7R^8$.

In one aspect of the invention R^7 and R^8 are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl and di(C_{1-3}alkyl)aminoC_{1-6}alkyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally NH and which ring is optionally substituted on carbon or nitrogen by a group selected from C_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl and hydroxyC_{1-4}alkoxyC_{1-4}alkyl, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$. In a further aspect R^7 and R^8 are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxy-1,1-dimethylpropyl, methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, allyl, propargyl, 2-(dimethylamino)ethyl and 2-(diethylamino)ethyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl, piperazinyl, diazepanyl and azetidinyl where the ring is optionally substituted by hydroxy, methyl, hydroxymethyl or 2-hydroxyethyl. In yet another aspect R^7 and R^8 are independently selected from hydrogen, ethyl, propyl, isobutyl, 3-hydroxy-1,1-dimethyl, 2-methoxyethyl, cyclobutyl and cyclopropylmethyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl and piperazinyl, where the ring is optionally substituted by hydroxymethyl or 2-hydroxyethyl.

In one aspect of the invention R^4 is hydrogen.

In one aspect of the invention R^5 is aryl optionally substituted by 1 or 2 halo. In another aspect R^5 is phenyl optionally substituted by 1 or 2 fluoro or chloro. In a further aspect R^5 is phenyl optionally substituted by 1 or 2 fluoro. In yet another aspect R^5 is 2,3-difluorophenyl or 3-fluorophenyl.

In one aspect of the invention $R^{3'}$ is $-X^{3'}R^{13'}$. In a further aspect $R^{3'}$ is selected from 3-[propyl(2-phosphonooxyethyl)amino]propoxy, 3-(2-phosphonooxymethylpyrrolidin-1-yl)propoxy, 3-[ethyl(2-phosphonooxyethyl)amino]propoxy, 3-[(2-methoxyethyl)(2-phosphonooxyethyl)amino]propoxy, 3-[cyclobutyl(2-phosphonooxyethyl)amino]propoxy, 3-

[4-(2-phosphonooxymethyl)piperazin-1-yl]propoxy and 3-[(1,1-dimethyl-3-phosphonooxypropyl)amino]propoxy.

In one aspect of the invention $X^{3'}$ is $-CH_2{=}CH_2-$, -O- or -NH-. In a further aspect $X^{3'}$ is -O-.

In one aspect of the invention $R^{13'}$ is C_{1-6}alkyl substituted by $-NR^{7'}R^{8'}$. In a further aspect of the invention $R^{13'}$ is propyl substituted by $-NR^{7'}R^{8'}$.

In one aspect of the invention $R^{7'}$ is selected from hydrogen, heterocyclyl, C_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, cyanoC_{1-4}alkyl and C_{3-6}cycloalkyl. In another aspect $R^{7'}$ is ethyl, propyl, cyclobutyl or 2-methoxyethyl.

In one aspect of the invention $R^{8'}$ is phosphonooxyC_{1-4}alkyl or phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl. In another aspect $R^{8'}$ is 2-phosphonooxyethyl or 1,1-dimethyl-3-phosphonooxypropyl.

In one aspect of the invention $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl and piperazinyl which ring is substituted on carbon or nitrogen by a group selected from phosphonooxy, phosponooxymethyl and 2-phoshonooxyethyl.

A preferred class of compounds is of formula (I) wherein:

X is NR^6;

R^6 is hydrogen or methyl;

R^1 is hydrogen or $-OR^{11}$;

X^1 is a direct bond or -O-;

R^{11} is hydrogen, heterocyclyl selected from piperidinyl or pyrrolidinyl, C_{1-4}alkyl optionally substituted by hydroxy, C_{1-4}alkoxy, amino, C_{1-4}alkylamino or di(C_{1-4}alkyl)amino;

R^2 is hydrogen or $-OR^{12}$;

R^{12} is hydrogen, C_{1-4}alkyl (optionally substituted by heterocyclyl) or heterocyclyl;

R^3 is $-X^3R^{13}$;

X^3 is $-CH_2{=}CH_2-$, -O- or -NH-;

R^{13} is C_{1-6}alkyl substituted by $-NR^7R^8$, heterocyclyl or halo;

R^7 and R^8 are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl and di(C_{1-3}alkyl)aminoC_{1-6}alkyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring

which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally NH and which ring is optionally substituted on carbon or nitrogen by a group selected from C_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl and hydroxyC_{1-4}alkoxyC_{1-4}alkyl, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$;

R^4 is hydrogen; and

R^5 is aryl optionally substituted by 1 or 2 halo.

A further preferred class of compounds is of formula (I) wherein:

X is NH;

R^1 is hydrogen;

R^2 is hydrogen or methoxy;

R^3 is $-X^3R^{13}$;

X^3 is -O-;

R^{13} is propyl substituted by chloro or $-NR^7R^8$;

R^7 and R^8 are independently selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxy-1,1-dimethylpropyl, methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, allyl, propargyl, 2-(dimethylamino)ethyl and 2-(diethylamino)ethyl; or R^7 and R^8 together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl, piperazinyl, diazepanyl and azetidinyl where the ring is optionally substituted by hydroxy, methyl, hydroxymethyl or 2-hydroxyethyl;

R^4 is hydrogen; and

R^5 is 2,3-difluorophenyl or 3-fluorophenyl.

A preferred class of compounds is of formula (IA) wherein:

X is NR^6;

R^6 is hydrogen or methyl;

R^1 is hydrogen or $-OR^{11}$;

R^{11} is hydrogen, heterocyclyl selected from piperidinyl or pyrrolidinyl, C_{1-4}alkyl optionally substituted by hydroxy, C_{1-4}alkoxy, amino, C_{1-4}alkylamino or di(C_{1-4}alkyl)amino;

R^2 is hydrogen or $-OR^{12}$;

R^{12} is hydrogen, C_{1-4}alkyl (optionally substituted with heterocyclyl) or heterocyclyl;

$R^{3'}$ is $-X^{3'}R^{13'}$;

$X^{3'}$ is $-CH_2{=}CH_2-$, -O- or -NH-;

$R^{13'}$ is C_{1-6}alkyl substituted by $-NR^{7'}R^{8'}$;

$R^{7'}$ is selected from hydrogen, heterocyclyl, C_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, cyanoC_{1-4}alkyl and C_{3-6}cycloalkyl;

$R^{8'}$ is phosphonooxyC_{1-4}alkyl or phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl;

or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl and piperazinyl which ring is substituted on carbon or nitrogen by a group selected from phosphonooxy, phosponooxymethyl and 2-phoshonooxyethyl;

R^4 is hydrogen; and

R^5 is aryl optionally substituted by 1 or 2 halo.

A further preferred class of compounds is of formula (IA) wherein:

X is NH;

R^1 is hydrogen;

R^2 is hydrogen or methoxy;

$R^{3'}$ is $-X^{3'}R^{13'}$;

$X^{3'}$ is -O-;

$R^{13'}$ is propyl substituted by $-NR^{7'}R^{8'}$;

$R^{7'}$ is ethyl, propyl, cyclobutyl or 2-methoxyethyl;

$R^{8'}$ is 2-phosphonooxyethyl or 1,1-dimethyl-3-phosphonooxypropyl;

or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring selected from pyrrolidinyl, piperidinyl and piperazinyl which ring is substituted on carbon or nitrogen by a group selected from phosphonooxy, phosponooxymethyl and 2-phoshonooxyethyl;

R^4 is hydrogen; and

R^5 is 2,3-difluorophenyl or 3-fluorophenyl.

Preferred compounds of the invention are any one of:

2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide;

2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-piperidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

2-[4-({7-[3-(diethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-[4-({7-[3-(cyclopropylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-[4-({7-[3-(4-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[ethyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(prop-2-yn-1-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[allyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[isobutyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-[4-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

2-{4-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-(4-{[7-(3-azetidin-1-ylpropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(dimethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-piperidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-[4-({7-[3-(cyclopropylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(4-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(prop-2-yn-1-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[isobutyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-[4-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclopentyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide; *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

{(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*S*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate;

{(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

{(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

2-{cyclobutyl[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-{cyclobutyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate;

2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate;

2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate;

2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate;

3-{[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}-3-methylbutyl dihydrogen phosphate;

3-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}-3-methylbutyl dihydrogen phosphate; and

{(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate.

In another aspect preferred compounds of the invention are any one of:

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide;

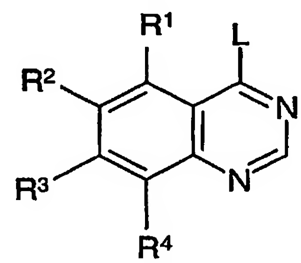
2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide;

N-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide; and

N-(3-fluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide.

Preferred compounds of formula (I) are those that are stable in mouse, rat, or human serum, preferably those that are stable in human serum.

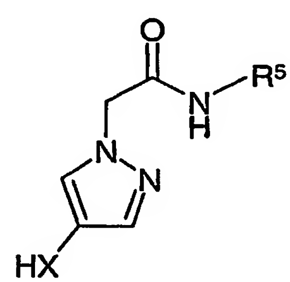
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof, which process comprises reacting a compound of formula (II)



(II)

where L is a suitable leaving group such as chloro, bromo, SMe etc.

with a compound of formula (III)



(III)

in the presence of hydrochloric acid in dioxane under an inert atmosphere,

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

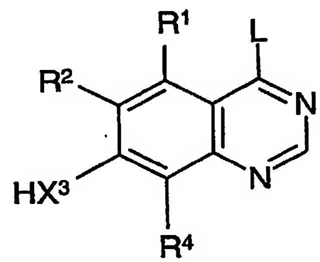
ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt, ester or prodrug thereof.

The reaction is suitably effected in an organic solvent such as dimethyl acetamide or

isopropanol at elevated temperatures of from 80°C to 120°C for 30 minutes to 2 hours.

The process may further comprise a process for the preparation of a compound of formula (II) when R^3 is $-X^3R^{13}$, which process comprises reacting a compound of formula (IV)



(IV)

with a compound of formula (V)

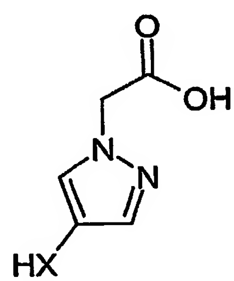
$$L^1\text{-}R^{13}$$

(V)

where L^1 is an appropriate leaving group such as chloro or L^1 is –OH which is suitably activated by a reagent such as PPh_3.

Compounds of formula (IV) and formula (V) are either known in the art or can be derived from other compounds known in the art by conventional methods which would be apparent from the literature.

The process may further comprise a process for the preparation of a compound of formula (III) which process comprises the reaction of a compound of formula (VI)



(VI)

with a compound of formula (VII)

$$R^5\text{-}NH_2$$

(VII)

The reaction is suitably effected in an organic solvent such as tetrahydrofuran (THF) or dichloromethane (DCM) at temperatures from 0°C to 25°C in the presence of a base such as pyridine under an inert atmosphere for 1 to 3 hours.

Further provided is a process for the preparation of a compound of formula (IA) or a pharmaceutically acceptable salt thereof, which process comprises phosphorylation of a suitable compound of formula (I) by reacting a compound of formula (I) and tetrazole with di-tert-butyl diethylphosphoramidite in an appropriate organic solvent such as dimethylformamide or dimethylacetamide under an inert atmosphere, followed by (after 1 to 5 hours) the addition of hydrogen peroxide and sodium metabisulphite. Deprotection of the phosphate group then yields a compound of formula (IA). Deprotection is suitably effected with hydrochloric acid in dioxane or dichloromethane (DCM) at ambient temperature for 6 to 30 hours.

Suitable reaction conditions are illustrated hereinafter.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof, as defined hereinbefore in association with a pharmaceutically acceptable diluent or carrier.

Also provided is a pharmaceutical composition which comprises a compound of formula (IA), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Therefore in a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof, for use in therapy. In addition a compound of formula (IA) or a pharmaceutically acceptable salt thereof is provided for use in therapy.

Further provided is a compound of formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof, for use as a medicament and also a compound of formula (IA), or a pharmaceutically acceptable salt thereof, for use as a medicament.

Additionally a compound of formula (I), or a pharmaceutically acceptable salt, ester or prodrug thereof is provided for use in a method of treatment of a warm-blooded animal such as man by therapy. A compound of formula (IA) or a pharmaceutically acceptable salt thereof is also provided for use in a method of treatment of a warm-blooded animal such as man by therapy.

In another aspect of the invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof, in the preparation of a

medicament for the treatment of a disease where the inhibition of one or more Aurora kinase(s) is beneficial. The use of a compound of formula (IA) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a disease where the inhibition of one or more Aurora kinase(s) is beneficial is also provided. In particular it is envisaged that inhibition of Aurora-A kinase and/or Aurora-B kinase may be beneficial.

In another aspect of the invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof, in the preparation of a medicament for the treatment of hyperproliferative diseases such as cancer and in particular colorectal, breast or pancreatic cancer. Also provided is the use of a compound of formula (IA) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of hyperproliferative diseases such as cancer and in particular colorectal, breast or pancreatic cancer.

According to yet another aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt ester or prodrug thereof for use in the method of treating a human suffering from a disease in which the inhibition of one or more Aurora kinases is beneficial, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof. Further provided is a compound of formula (IA) or a pharmaceutically acceptable salt thereof for use in the method of treating a human suffering from a disease in which the inhibition of one or more Aurora kinases is beneficial, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (IA) or a pharmaceutically acceptable salt thereof. In particular it is envisaged that inhibition of Aurora-A kinase and/or Aurora-B kinase may be beneficial.

Further provided is a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the method of treating a human suffering from a hyperproliferative disease such as cancer and in particular colorectal, breast or pancreatic cancer, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof. A compound of formula (IA) is also provided for use in the method of treating a human suffering from a hyperproliferative disease such as cancer and in particular colorectal, breast or pancreatic cancer, comprising the steps of administering to a person in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

For the above mentioned therapeutic uses the dose administered will vary with the

compound employed, the mode of administration, the treatment desired, the disorder indicated and the age and sex of the animal or patient. The size of the dose would thus be calculated according to well known principles of medicine.

In using a compound of formula (I) or formula (IA) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.05 mg/kg to 50 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used.

The treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestratrant); antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]) , farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine-threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor,

approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

In addition to their use in therapeutic medicine, a compound of formula (I) and a pharmaceutically acceptable salt, ester or prodrug thereof are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

The compounds of the invention inhibit the serine-threonine kinase activity of the Aurora kinases, in particular Aurora-A kinase and/or Aurora-B kinase and thus inhibit the cell cycle and cell proliferation. These properties may be assessed for example, using one or more of the procedures set out below.

(a) In Vitro Aurora-A kinase inhibition test

This assay determines the ability of a test compound to inhibit serine-threonine kinase activity. DNA encoding Aurora-A may be obtained by total gene synthesis or by cloning. This DNA may then be expressed in a suitable expression system to obtain polypeptide with serine-threonine kinase activity. In the case of Aurora-A, the coding sequence was isolated from cDNA by polymerase chain reaction (PCR) and cloned into the BamH1 and Not1 restriction endonuclease sites of the baculovirus expression vector pFastBac HTc (GibcoBRL/Life technologies). The 5' PCR primer contained a recognition sequence for the restriction endonuclease BamH1 5' to the Aurora-A coding sequence. This allowed the insertion of the Aurora-A gene in frame with the 6 histidine residues, spacer region and rTEV protease cleavage site encoded by the pFastBac HTc vector. The 3' PCR primer replaced the Aurora-A stop codon with additional coding sequence followed by a stop codon and a recognition sequence for the restriction endonuclease Not1. This additional coding sequence (5' TAC

CCA TAC GAT GTT CCA GAT TAC GCT TCT TAA 3') encoded for the polypeptide sequence YPYDVPDYAS. This sequence, derived from the influenza hemagglutin protein, is frequently used as a tag epitope sequence that can be identified using specific monoclonal antibodies. The recombinant pFastBac vector therefore encoded for an N-terminally 6 his tagged, C terminally influenza hemagglutin epitope tagged Aurora-A protein. Details of the methods for the assembly of recombinant DNA molecules can be found in standard texts, for example Sambrook et al. 1989, Molecular Cloning - A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory press and Ausubel et al. 1999, Current Protocols in Molecular Biology, John Wiley and Sons Inc.

Production of recombinant virus can be performed following manufacturer's protocol from GibcoBRL. Briefly, the pFastBac-1 vector carrying the Aurora-A gene was transformed into E. coli DH10Bac cells containing the baculovirus genome (bacmid DNA) and via a transposition event in the cells, a region of the pFastBac vector containing gentamycin resistance gene and the Aurora-A gene including the baculovirus polyhedrin promoter was transposed directly into the bacmid DNA. By selection on gentamycin, kanamycin, tetracycline and X-gal, resultant white colonies should contain recombinant bacmid DNA encoding Aurora-A. Bacmid DNA was extracted from a small scale culture of several BH10Bac white colonies and transfected into Spodoptera frugiperda Sf21 cells grown in TC100 medium (GibcoBRL) containing 10% serum using CellFECTIN reagent (GibcoBRL) following manufacturer's instructions. Virus particles were harvested by collecting cell culture medium 72 hrs post transfection. 0.5 mls of medium was used to infect 100 ml suspension culture of Sf21s containing 1 x 10^7 cells/ml. Cell culture medium was harvested 48 hrs post infection and virus titre determined using a standard plaque assay procedure. Virus stocks were used to infect Sf9 and "High 5" cells at a multiplicity of infection (MOI) of 3 to ascertain expression of recombinant Aurora-A protein.

For the large scale expression of Aurora-A kinase activity, Sf21 insect cells were grown at 28°C in TC100 medium supplemented with 10% foetal calf serum (Viralex) and 0.2% F68 Pluronic (Sigma) on a Wheaton roller rig at 3 r.p.m. When the cell density reached 1.2×10^6 cells ml^{-1} they were infected with plaque-pure Aurora-A recombinant virus at a multiplicity of infection of 1 and harvested 48 hours later. All subsequent purification steps were performed at 4°C. Frozen insect cell pellets containing a total of 2.0 x 10^8 cells were thawed and diluted with lysis buffer (25 mM HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-

ethanesulphonic acid]) pH7.4 at 4°C , 100 mM KCl, 25 mM NaF, 1 mM Na_3VO_4, 1 mM PMSF (phenylmethylsulphonyl fluoride), 2 mM 2-mercaptoethanol, 2 mM imidazole, 1 μg/ml aprotinin, 1 μg/ml pepstatin, 1 μg/ml leupeptin), using 1.0 ml per 3 x 10^7 cells. Lysis was achieved using a dounce homogeniser, following which the lysate was centrifuged at 41,000*g* for 35 minutes. Aspirated supernatant was pumped onto a 5 mm diameter chromatography column containing 500 μl Ni NTA (nitrilo-tri-acetic acid) agarose (Qiagen, product no. 30250) which had been equilibrated in lysis buffer. A baseline level of UV absorbance for the eluent was reached after washing the column with 12 ml of lysis buffer followed by 7 ml of wash buffer (25 mM HEPES pH7.4 at 4°C , 100 mM KCl, 20 mM imidazole, 2 mM 2-mercaptoethanol). Bound Aurora-A protein was eluted from the column using elution buffer (25 mM HEPES pH7.4 at 4°C , 100 mM KCl, 400 mM imidazole, 2 mM 2-mercaptoethanol). An elution fraction (2.5 ml) corresponding to the peak in UV absorbance was collected. The elution fraction, containing active Aurora-A kinase, was dialysed exhaustively against dialysis buffer (25 mM HEPES pH7.4 at 4°C , 45% glycerol (v/v), 100 mM KCl, 0.25% Nonidet P40 (v/v), 1 mM dithiothreitol).

Each new batch of Aurora-A enzyme was titrated in the assay by dilution with enzyme diluent (25mM Tris-HCl pH7.5, 12.5mM KCl, 0.6mM DTT). For a typical batch, stock enzyme is diluted 1 in 666 with enzyme diluent & 20μl of dilute enzyme is used for each assay well. Test compounds (at 10mM in dimethylsulphoxide (DMSO) were diluted with water & 10μl of diluted compound was transferred to wells in the assay plates. "Total" & "blank" control wells contained 2.5% DMSO instead of compound. Twenty microlitres of freshly diluted enzyme was added to all wells, apart from "blank" wells. Twenty microlitres of enzyme diluent was added to "blank" wells. Twenty microlitres of reaction mix (25mM Tris-HCl, 78.4mM KCl, 2.5mM NaF, 0.6mM dithiothreitol, 6.25mM $MnCl_2$, 6.25mM ATP, 7.5μM peptide substrate [biotin-LRRWSLGLRRWSLGLRRWSLGLRRWSLG]) containing 0.2μCi [γ^{33}P]ATP (Amersham Pharmacia, specific activity ≥2500Ci/mmol) was then added to all test wells to start the reaction. The plates were incubated at room temperature for 60 minutes. To stop the reaction 100μl 20% v/v orthophosphoric acid was added to all wells. The peptide substrate was captured on positively-charged nitrocellulose P30 filtermat (Whatman) using a 96-well plate harvester (TomTek) & then assayed for incorporation of ^{33}P with a Beta plate counter. "Blank" (no enzyme) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

In this test, the compounds of the invention generally give 50% inhibition of enzyme activity at concentrations of 1nM to 1000nM and in particular compound 16 in Table 2 gave 50% inhibition of enzyme activity at a concentration of 34nM, compound 47 in Table 3 gave 50% inhibition of enzyme activity at a concentration of 10nM and compound 97 in Table 5 gave 50% inhibition of enzyme activity at a concentration of 0.5μM

(b) In Vitro Aurora-B kinase inhibition test

This assay determines the ability of a test compound to inhibit serine-threonine kinase activity. DNA encoding Aurora-B may be obtained by total gene synthesis or by cloning. This DNA may then be expressed in a suitable expression system to obtain polypeptide with serine-threonine kinase activity. In the case of Aurora-B, the coding sequence was isolated from cDNA by polymerase chain reaction (PCR) and cloned into the pFastBac system in a manner similar to that described above for Aurora-A (i.e. to direct expression of a 6-histidine tagged Aurora-B protein).

For the large scale expression of Aurora-B kinase activity, Sf21 insect cells were grown at 28°C in TC100 medium supplemented with 10% foetal calf serum (Viralex) and 0.2% F68 Pluronic (Sigma) on a Wheaton roller rig at 3 r.p.m. When the cell density reached $1.2x10^6$ cells ml^{-1} they were infected with plaque-pure Aurora-B recombinant virus at a multiplicity of infection of 1 and harvested 48 hours later. All subsequent purification steps were performed at 4°C. Frozen insect cell pellets containing a total of 2.0×10^8 cells were thawed and diluted with lysis buffer (50 mM HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid]) pH7.5 at 4°C , 1 mM Na_3VO_4, 1 mM PMSF (phenylmethylsulphonyl fluoride), 1 mM dithiothreitol, 1 μg/ml aprotinin, 1 μg/ml pepstatin, 1 μg/ml leupeptin), using 1.0 ml per 2×10^7 cells. Lysis was achieved using a sonication homogeniser, following which the lysate was centrifuged at 41,000g for 35 minutes. Aspirated supernatant was pumped onto a 5 mm diameter chromatography column containing 1.0 ml CM sepharose Fast Flow (Amersham Pharmacia Biotech) which had been equilibrated in lysis buffer. A baseline level of UV absorbance for the eluent was reached after washing the column with 12 ml of lysis buffer followed by 7 ml of wash buffer (50 mM HEPES pH7.4 at 4°C , 1 mM dithiothreitol). Bound Aurora-B B protein was eluted from the column using a gradient of elution buffer (50 mM HEPES pH7.4 at 4°C , 0.6 M NaCl, 1 mM dithiothreitol, running from 0% elution buffer to 100% elution buffer over 15 minutes at a flowrate of 0.5 ml/min). Elution fractions (1.0 ml)

corresponding to the peak in UV absorbance was collected. Elution fractions were dialysed exhaustively against dialysis buffer (25 mM HEPES pH7.4 at 4°C , 45% glycerol (v/v), 100 mM KCl, 0.05% (v/v) IGEPAL CA630 (Sigma Aldrich), 1 mM dithiothreitol). Dialysed fractions were assayed for Aurora-B kinase activity.

Each new batch of Aurora-B enzyme was titrated in the assay by dilution with enzyme diluent (25mM Tris-HCl pH7.5, 12.5mM KCl, 0.6mM DTT). For a typical batch, stock enzyme is diluted 1 in 40 with enzyme diluent & 20µl of dilute enzyme is used for each assay well. Test compounds (at 10mM in dimethylsulphoxide (DMSO) were diluted with water & 10µl of diluted compound was transferred to wells in the assay plates. "Total" & "blank" control wells contained 2.5% DMSO instead of compound. Twenty microlitres of freshly diluted enzyme was added to all wells, apart from "blank" wells. Twenty microlitres of enzyme diluent was added to "blank" wells. Twenty microlitres of reaction mix (25mM Tris-HCl, 78.4mM KCl, 2.5mM NaF, 0.6mM dithiothreitol, 6.25mM $MnCl_2$, 37.5mM ATP, 25µM peptide substrate [biotin-LRRWSLGLRRWSLGLRRWSLGLRRWSLG]) containing 0.2µCi [γ^{33}P]ATP (Amersham Pharmacia, specific activity ≥2500Ci/mmol) was then added to all test wells to start the reaction. The plates were incubated at room temperature for 60 minutes. To stop the reaction 100µl 20% v/v orthophosphoric acid was added to all wells. The peptide substrate was captured on positively-charged nitrocellulose P30 filtermat (Whatman) using a 96-well plate harvester (TomTek) & then assayed for incorporation of ^{33}P with a Beta plate counter. "Blank" (no enzyme) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity. In this test, the compounds of the invention generally give 50% inhibition of enzyme activity at concentrations of 1nM to 1000nM and in particular compound 16 in Table 2 gave 50% inhibition of enzyme activity at a concentration of 5nM, compound 47 in Table 3 gave 50% inhibition of enzyme activity at a concentration of 8nM and compound 97 in Table 5 gave 50% inhibition of enzyme activity at a concentration of 9nM.

(c) <u>In Vitro cell proliferation assay</u>

This and other assays can be used to determine the ability of a test compound to inhibit the growth of adherent mammalian cell lines, for example the human tumour cell line SW620 (ATCC CCL-227). This assay determines the ability of at test compound to inhibit the incorporation of the thymidine analogue, 5'-bromo-2'-deoxy-uridine (BrdU) into cellular

DNA. SW620 or other adherent cells were typically seeded at $1x10^5$ cells per well in L-15 media (GIBCO) plus 5% foetal calf serum, 1% L-glutamine (100µl / well) in 96 well tissue culture treated 96 well plates (Costar) and allowed to adhere overnight. The following day the cells were dosed with compound (diluted from 10mM stock in DMSO using L-15 (with 5% FCS, 1% L-glutamine). Untreated control wells and wells containing a compound known to give 100% inhibition of BrdU incorporation were included on each plate. After 48 hours in the presence / absence of test compound the ability of the cells to incorporate BrdU over a 2 hour labelling period was determined using a Boehringer (Roche) Cell Proliferation BrdU ELISA kit (cat. No. 1 647 229) according to manufacturers directions. Briefly, 15µl of BrdU labelling reagent (diluted 1:100 in media – L-15, 5% FCS, 1% L-glutamine) was added to each well and the plate returned to a humidified (+5% CO_2) 37°C incubator for 2 hours. After 2 hours the labelling reagent was removed by decanting and tapping the plate on a paper towel. FixDenat solution (50µl per well) was added and the plates incubated at room temperature for 45mins with shaking. The FixDenat solution was removed by decanting and tapping the inverted plate on a paper towel. The plate was then washed once with phosphate buffered saline (PBS) and 100µl /well of Anti-BrdU-POD antibody solution (diluted 1:100 in antibody dilution buffer) added. The plate was then incubated at room temperature with shaking for 90min. Unbound Anti-BrdU-POD antibody was removed by decanting and washing the plate 4 times with PBS before being blotted dry. TMB substrate solution was added (100µl/well) and incubated for approximately 10 minutes at room temperature with shaking until a colour change was apparent. The optical density of the wells was then determined at 690nm wavelength using a Titertek Multiscan plate reader. The values from compound treated, untreated and 100% inhibition controls were used to determine the dilution range of a test compound that gave 50% inhibition of BrdU incorporation. The compounds of the invention are generally active at 1nM to 100µM in this test and in particular compound 16 in Table 2 gave 50% inhibition of enzyme activity at a concentration of 10nM, compound 47 in Table 3 gave 50% inhibition of enzyme activity at a concentration of 1nM and compound 97 in Table 5 gave 50% inhibition of enzyme activity at a concentration of 1nM.

(d) <u>In Vitro cell cycle analysis assay</u>

This assay determines the ability of a test compound to arrest cells in specific phases of the cell cycle. Many different mammalian cell lines could be used in this assay and SW620 cells are included here as an example. SW620 cells were seeded at 7 x 10^5 cells per T25 flask (Costar) in 5 ml L-15 (5% FCS, 1% L-glutamine). Flasks were then incubated overnight in a humidified 37^0C incubator with 5% CO_2. The following day, 5µl of L-15 (5% FCS, 1% L-glutamine) carrying the appropriate concentration of test compound solubilised in DMSO was added to the flask. A no compound control treatment was also included (0.5% DMSO). The cells were then incubated for a defined time (24 hours) with compound. After this time the media was aspirated from the cells and they were washed with 5ml of prewarmed (37^0C) sterile PBSA, then detached from the flask by brief incubation with trypsin and followed by resuspension in 5ml of 1% Bovine Serum Albumin (BSA, Sigma-Aldrich Co.) in sterile PBSA. The samples were then centrifuged at 2200rpm for 10 min. The supernatant was aspirated to leave 200µl of the PBS/BSA solution. The pellet was resuspended in this 200µl of solution by pipetting 10 times to create a single cell suspension. One ml of ice-cold 80% ethanol was slowly added to each cell suspension and the samples stored at -20°C overnight or until required for staining. Cells were pelleted by centrifugation, ethanol aspirated off and pellets resuspended in 200µl PBS containing 100µg/ml RNAse (Sigma Aldrich) & 10µg/ml Propidium Iodide (Sigma Aldrich). Cell suspensions were incubated at 37°C for 30min, a further 200µl PBS added and samples stored in the dark at 4°C overnight.

Each sample was then syringed 10 times using 21-guage needle. The samples were then transferred to LPS tubes and DNA content per cell analysed by Fluorescence activated cell sorting (FACS) using a FACScan flow cytometer (Becton Dickinson). Typically 30,000 events were counted and recorded using CellQuest v1.1 software (Verity Software). Cell cycle distribution of the population was calculated using Modfit software (Verity Software) and expressed as percentage of cells with 2N (G0/G1), 2N-4N (S phase) and with 4N (G2/M) DNA content.

The compounds of the invention are generally active in this test at 1nM to 10µM and in particular in particular compound 16 in Table 2 gave 50% inhibition of enzyme activity at a concentration of 7nM, compound 47 in Table 3 gave 50% inhibition of enzyme activity at a concentration of 3nM and compound 97 in Table 5 gave 50% inhibition of enzyme activity at a concentration of 21nM.

The invention will now be illustrated in the following non limiting examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these examples may be used where appropriate, and in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation *in vacuo* and work up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, typically in the range 18-25°C and in air unless stated, or unless the skilled person would otherwise operate under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385);

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured in deuterated dimethyl sulphoxide (DMSO d_6) (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane) using one of the following four instruments

- Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz
- Bruker DPX300 spectrometer operating at a field strength of 300MHz
- JEOL EX 400 spectrometer operating at a field strength of 400 MHz
- Bruker Avance 500 spectrometer operating at a field strength of 500MHz

Peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; qu, quintet; m, multiplet; br s, broad singlet;

(vi) robotic synthesis was carried out using a Zymate XP robot, with solution additions via a Zymate Master Laboratory Station and stirred via a Stem RS5000 Reacto-Station at 25°C;

(vii) work up and purification of reaction mixtures from robotic synthesis was carried out as follows: evaporations were carried out *in vacuo* using a Genevac HT 4; column chromatography was performed using either an Anachem Sympur MPLC system on silica using 27 mm diameter columns filled with Merck silica (60 μm, 25 g); the structures of the final products were confirmed by LCMS on a Waters 2890 / ZMD micromass system using the following and are quoted as retention time (RT) in minutes:

Column:	waters symmetry C18 3.5 μm 4.6x50 mm
Solvent A:	H_2O

Solvent B:	CH_3CN
Solvent C :	MeOH + 5% HCOOH
Flow rate:	2.5 ml / min
Run time:	5 minutes with a 4.5 minute gradient from 0-100% C
Wavelength:	254 nm, bandwidth 10 nm
Mass detector:	ZMD micromass
Injection volume	0.005 ml

(viii) Analytical LCMS for compounds which had not been prepared by robotic synthesis was performed on a Waters Alliance HT system using the following and are quoted as retention time (RT) in minutes:

Column:	2.0 mm x 5 cm Phenomenex Max-RP 80A
Solvent A:	Water
Solvent B:	Acetonitrile
Solvent C:	Methanol / 1% formic acid or Water / 1% formic acid
Flow rate:	1.1 ml / min
Run time:	5 minutes with a 4.5 minute gradient from 0-95% B + constant 5% solvent C
Wavelength:	254 nm, bandwidth 10 nm
Injection volume	0.005 ml
Mass detector:	Micromass ZMD

(ix) Preparative high performance liquid chromatography (HPLC) was performed on either

- Waters preparative LCMS instrument, with retention time (RT) measured in minutes:

Column:	β-basic Hypercil (21x100 mm) 5μm
Solvent A:	Water / 0.1% Ammonium carbonate
Solvent B:	Acetonitrile
Flow rate:	25 ml / min
Run time:	10 minutes with a 7.5 minute gradient from 0-100% B
Wavelength:	254 nm, bandwidth 10 nm
Injection volume	1 - 1.5 ml
Mass detector :	Micromass ZMD

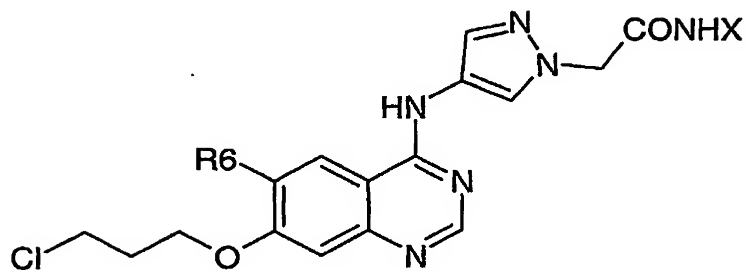
- Gilson preparative HPLC instrument, with retention time (RT) measured in minutes:

Column:	21 mm x 15 cm Phenomenex Luna2 C18

Solvent A:	Water + 0.1% trifluoracetic acid,
Solvent B:	Acetonitrile + 0.1% trifluoracetic acid
Flow rate:	21 ml / min
Run time:	20 minutes with various 10 minute gradients from 5-100% B
Wavelength:	254 nm, bandwidth 10 nm
Injection volume	0.1-4.0 ml

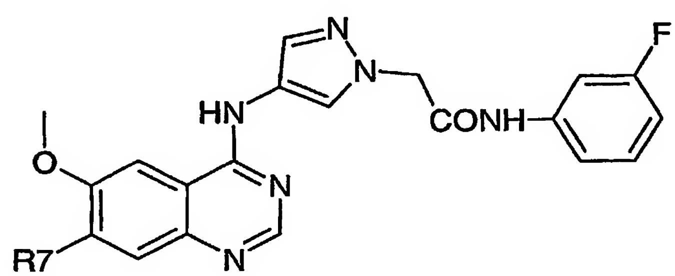
(x) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis.

Table 1



Compound	R6	X
1	OMe	3-fluorophenyl
2	H	2,3-difluorophenyl
3	OMe	2,3-difluorophenyl
4	H	3-fluorophenyl

Table 2

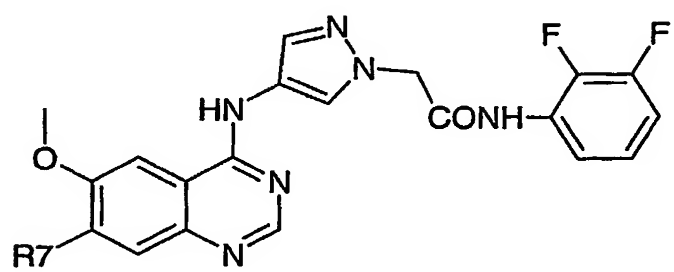


Compound	R7
5	3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
6	3-[(2-hydroxyethyl)(isobutyl)amino]propoxy
7	3-[(2-hydroxyethyl)(propyl)amino]propoxy
8	3-piperidin-1-ylpropoxy
9	3-pyrrolidin-1-ylpropoxy
10	3-(diethylamino)propoxy
11	3-piperazin-1-ylpropoxy
12	3-[(2-hydroxyethyl)(methyl)amino]propoxy

13	3-(cyclopropylamino)propoxy
14	3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy
15	3-(4-methylpiperazin-1-yl)propoxy
16	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
17	3-(4-hydroxypiperidin-1-yl)propoxy
18	3-[bis(2-hydroxyethyl)amino]propoxy
19	3-[ethyl(methyl)amino]propoxy
20	3-[ethyl(2-hydroxyethyl)amino]propoxy
21	3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy
22	3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy
23	3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy
24	3-[(cyclopropylmethyl)amino]propoxy
25	3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy
26	3-[methyl(prop-2-yn-1-yl)amino]propoxy
27	3-[allyl(methyl)amino]propoxy
28	3-[isobutyl(methyl)amino]propoxy
29	3-(3-hydroxypiperidin-1-yl)propoxy
30	3-[4-(hydroxymethyl)piperidin-1-yl]propoxy
31	3-[methyl(propyl)amino]propoxy
32	3-[(cyclopropylmethyl)(propyl)amino]propoxy
33	3-[[2-(diethylamino)ethyl](methyl)amino]propoxy
34	3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy
35	3-(4-methyl-1,4-diazepan-1-yl)propoxy
36	3-[(2-hydroxyethyl)(isopropyl)amino]propoxy
37	3-[cyclopropyl(2-hydroxyethyl)amino]propoxy
38	3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy
39	3-[cyclobutyl(2-hydroxyethyl)amino]propoxy
40	3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy

41	3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy
42	3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy
43	3-[allyl(2-hydroxyethyl)amino]propoxy
44	3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy
45	3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy
46	3-azetidin-1-ylpropoxy

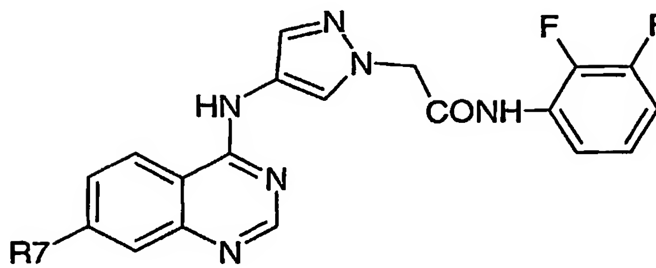
Table 3



Compound	R7
47	3-[(2-hydroxyethyl)(isobutyl)amino]propoxy
48	3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
49	3-[(2-hydroxyethyl)(propyl)amino]propoxy
50	3-(dimethylamino)propoxy
51	3-piperidin-1-ylpropoxy
52	3-pyrrolidin-1-ylpropoxy
53	3-piperazin-1-ylpropoxy
54	3-[(2-hydroxyethyl)(methyl)amino]propoxy
55	3-(cyclopropylamino)propoxy
56	3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy
57	3-(4-methylpiperazin-1-yl)propoxy
58	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
59	3-(4-hydroxypiperidin-1-yl)propoxy

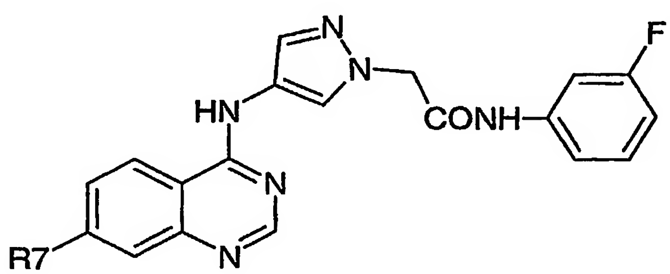
60	3-[bis(2-hydroxyethyl)amino]propoxy
61	3-[ethyl(methyl)amino]propoxy
62	3-[ethyl(2-hydroxyethyl)amino]propoxy
63	3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy
64	3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy
65	3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy
66	3-[(cyclopropylmethyl)amino]propoxy
67	3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy
68	3-[methyl(prop-2-yn-1-yl)amino]propoxy
69	3-[isobutyl(methyl)amino]propoxy
70	3-(3-hydroxypiperidin-1-yl)propoxy
71	3-[4-(hydroxymethyl)piperidin-1-yl]propoxy
72	3-[methyl(propyl)amino]propoxy
73	3-[(cyclopropylmethyl)(propyl)amino]propoxy
74	3-[[2-(diethylamino)ethyl](methyl)amino]propoxy
75	3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy
76	3-(4-methyl-1,4-diazepan-1-yl)propoxy
77	3-[(2-hydroxyethyl)(isopropyl)amino]propoxy
78	3-[cyclopropyl(2-hydroxyethyl)amino]propoxy
79	3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy
80	3-[cyclobutyl(2-hydroxyethyl)amino]propoxy
81	3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy
82	3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy
83	3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy
84	3-[allyl(2-hydroxyethyl)amino]propoxy
85	3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy
86	3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy

Table 4



Compound	R7
87	3-[(2-hydroxyethyl)(propyl)amino]propoxy
88	3-[(2-hydroxyethyl)(isobutyl)amino]propoxy
89	3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
90	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy
91	3-[(2-hydroxyethyl)(cyclopentyl)amino]propoxy
92	3-[(2-hydroxyethyl)(ethyl)amino]propoxy
93	3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy
94	3-[4-(hydroxymethyl)piperidin-1-yl]propoxy
95	3-[(3-hydroxy-1,1 dimethylpropyl)amino]propoxy

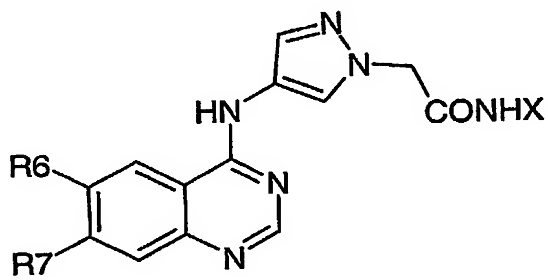
Table 5

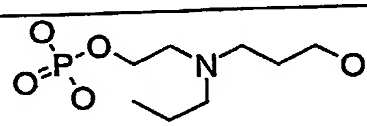
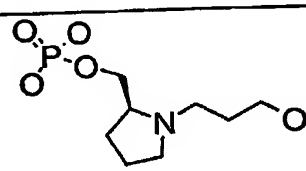
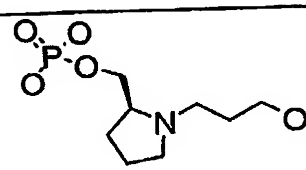
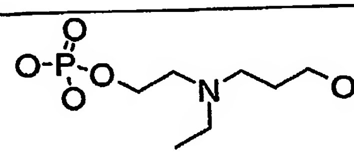
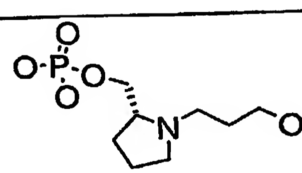


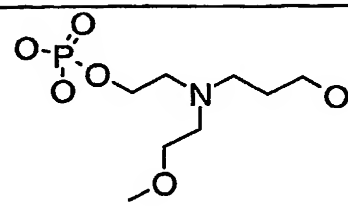
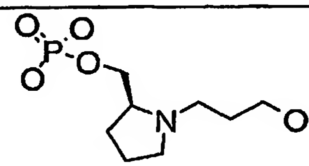
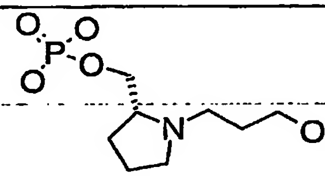
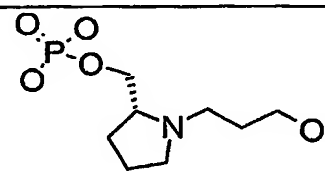
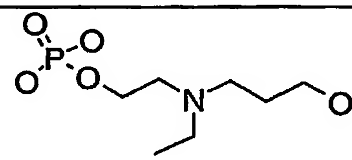
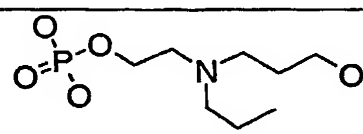
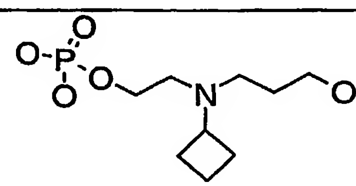
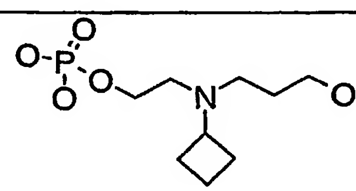
Compound	R7
96	3-[(2-hydroxyethyl)(propyl)amino]propoxy
97	3-[(2-hydroxyethyl)(ethyl)amino]propoxy
98	3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy

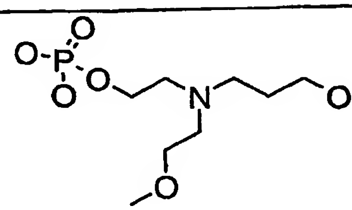
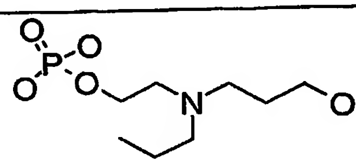
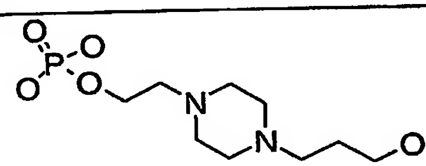
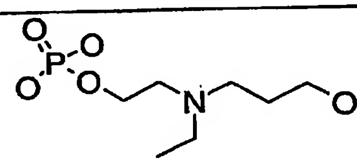
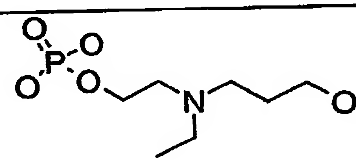
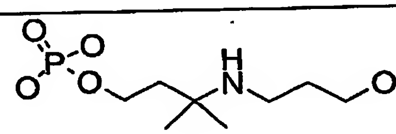
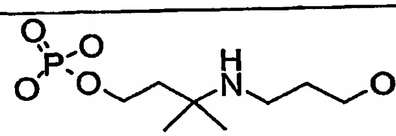
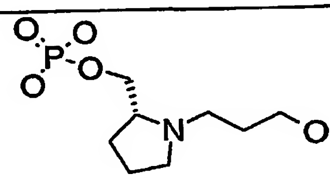
99	3-[4-(hydroxymethyl)piperidin-1-yl]propoxy
100	3-[(3-hydroxy-1,1 dimethylpropyl)amino]propoxy

Table 6



Compound	R6	R7	X
101	OMe		2,3-difluorophenyl
102	OMe		2,3-difluorophenyl
103	OMe		3-fluorophenyl
104	OMe		3-fluorophenyl
105	OMe		3-fluorophenyl

106	OMe		2,3-difluorophenyl
107	H		2,3-difluorophenyl
108	H		2,3-difluorophenyl
109	OMe		2,3-difluorophenyl
110	OMe		2,3-difluorophenyl
111	H		2,3-difluorophenyl
112	OMe		2,3-difluorophenyl
113	OMe		3-fluorophenyl

114	OMe		3-fluorophenyl
115	H		3-fluorophenyl
116	H		2,3-difluorophenyl
117	H		3-fluorophenyl
118	H		2,3-difluorophenyl
119	H		3-fluorophenyl
120	H		2,3-difluorophenyl
121	H		3-fluorophenyl

Example 1 - Preparation of compound 1 in table 1 - 2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide

A solution of 4.0 N hydrochloric acid in dioxane (250 µl) was added to a suspension of 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (234 mg, 1 mmol) and 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline (287 mg, 1 mmol) in dimethylacetamide (5 ml) and reaction mixture heated at 90 °C under argon for 0.5 hours. The mixture was cooled to ambient temperature, diluted with dichloromethane (16 ml) and the resultant precipitate filtered. The solid was washed with dichloromethane, diethyl ether and dried *in vacuo* to yield compound 1 in table 1 (495 mg, 95 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.39 (s, 1H), 8.09 (s, 1H), 7.95 (s, 1H), 7.61 (d, 1H), 7.38 (m, 2H), 7.33 (s, 1H), 6.92 (t, 1H), 5.15 (s, 2H), 4.33 (t, 2H), 4.03 (s, 3H), 3.84 (t, 2H), 2.32 (m, 2H).

MS (+ve ESI): 485.1, 487.2 $(M+H)^+$

2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide used as starting material, was obtained as follows:

a) A solution of phosphorus oxychloride (668 mg, 4.40 mmol) in tetrahydrofuran (4 ml) was added to a mixture of (4-nitro-1H-pyrazol-1-yl)acetic acid (684 mg, 4.00 mmol), 3-fluoroaniline (500 mg, 4.5 mmol) and pyridine (1.26 g, 16 mmol) in tetrahydrofuran (20 ml) at 0 °C under argon. The resulting mixture was stirred for 1 hour and an aqueous solution of sodium bicarbonate (20 ml) added. The mixture was further diluted with water and extracted with ethyl acetate (3 x 50 ml). The organic phase was recovered, dried and concentrated to give an oil which was triturated with diethyl ether : petroleum ether (1:1) to yield *N*-(3-fluorophenyl)-2-(4-nitro-1*H*-pyrazol-1-yl)acetamide (695 mg, 65 % yield):

^{1}H-NMR (DMSO d_6): 8.93 (s, 1H), 8.33 (s, 1H), 7.51 (dd, 1H), 7.38 (q, 1H), 7.31 (d, 1H), 6.95 (t, 1H), 5.17 (s, 2H).

MS (+ve ESI): 265.2 $(M+H)^+$

b) A solution of *N*-(3-fluorophenyl)-2-(4-nitro-1*H*-pyrazol-1-yl)acetamide (634 mg, 2.40 mmol) and platinum oxide (126 mg) in ethanol : ethyl acetate (1:4, 50 ml) was stirred under an atmosphere of hydrogen (80 psi) for 3 hours. The catalyst was removed by filtration and the residue purified by silica gel chromatography. Elution with dichloromethane : methanol (9:1 to 8:2) followed by dichloromethane : methanolic ammonia (3 N) (9:1) gave an oil which was

triturated with diethyl ether to yield 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (350 mg, 62 % yield):

^{1}H-NMR (DMSO d_6): 7.57 (d, 1H), 7.35 (q, 1H), 7.29 (d, 1H), 7.09 (s, 1H), 6.96 (s, 1H), 6.91 (t, 1H), 5.77 (s, 2H), 4.82 (br s, 2H).

MS (+ve ESI): 235.3 $(M+H)^+$

4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline used as starting material, was obtained as follows:

a) Palladium on carbon (3.3g of a 10 % mixture) was added to a solution of 7-(benzyloxy)-6-methoxyquinazolin-4-(3H)-one (20 g, 71 mmol) (prepared according to *J. Med. Chem.* **1999**, *42*, 5369-5389) was suspended in dimethylformamide (530 ml). Ammonium formate (45 g, 710 mmol) was then added portion wise over 1.25 hours. The reaction mixture was stirred for an additional 0.5 hours and the catalyst was removed by filtration. The solvent was removed *in vacuo* to yield 7-hydroxy-6-methoxyquinazolin-4-(3H)-one (8.65 g, 64 % yield):

^{1}H-NMR (DMSO d_6): 7.91 (s, 1H), 7.45 (s, 1H), 7.01 (s, 1H), 3.90 (s, 3H).

b) A mixture of 7-hydroxy-6-methoxyquinazolin-4-(3H)-one (8.0 g, 41.6 mmol), pyridine (7.5 ml) and acetic anhydride (63 ml) was heated at 100 °C for 4.5 hours and left to cool to ambient temperature 18 hours. The reaction mixture was poured into ice/water (400 ml) and the resultant precipitate collected by filtration and dried *in vacuo*. Analysis revealed that hydrolysis of the acetate group on the 4 position of the quinazoline was incomplete. The mixture was therefore treated with water (150 ml) and pyridine (0.5 ml) at 90 °C for 15 minutes. The reaction was cooled and the solid was collected by filtration, washed with water and dried *in vacuo* to yield 7-(acetoxy)-6-methoxyquinazolin-4-(3H)-one (7.4 g, 76 % yield):

^{1}H-NMR (DMSO d_6): 8.05 (s, 1H), 7.65 (s, 1H), 7.45 (s, 1H), 3.90 (s, 3H), 2.31 (s, 3H).

c) Dimethylformamide (0.5 ml) was added to a solution of 7-(acetoxy)-6-methoxyquinazolin-4-(3H)-one (2.0 g, 8.5 mmol) in thionyl chloride (32 ml) and the reaction mixture was heated at reflux for 1.5 hours. Upon cooling to ambient temperature, the thionyl chloride was removed *in vacuo* and azeotroped twice with toluene. The residue was diluted with dichloromethane (15 ml), a solution of 10 % ammonia in methanol (80 ml) added and the mixture heated at 80 °C for 10 minutes. Upon cooling to ambient temperature, the solvent was

evaporated to almost complete dryness, water was added and the pH adjusted to 7 with dilute hydrochloric acid. The resultant precipitate was collected by filtration and dried *in vacuo* at 35 °C for 18 hours to yield 4-chloro-7-hydroxy-6-methoxyquinazoline (1.65 g, 92 % yield):
^{1}H-NMR (DMSO d_6): 8.81 (s, 1H), 7.40 (s, 1H), 7.25 (s, 1H), 4.00 (s, 3H).

d) Triphenylphosphine (2.6 g, 10.1 mmol) and 3-chloropropanol (0.69 ml, 8.2 mmol) were added to a suspension of 4-chloro-7-hydroxy-6-methoxyquinazoline (1.65 g, 7.8 mmol) in dichloromethane (100 ml) under argon. The flask was placed in a water bath at 20 °C and di-*tert*butyl azodicarboxylate (2.30 g, 10.1 mmol) added portion wise over a few minutes. The reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was concentrated and the solution loaded directly onto a silica chromatography column. Elution with ethyl acetate : petroleum ether (3:7), yielded 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline (2.0 g, 91 % yield):
^{1}H-NMR (DMSO d_6): 8.90 (s, 1H), 7.55 (s, 1H), 7.45 (s, 1H), 4.42 (m, 2H), 4.05 (s, 3H), 3.80 (m, 2H), 2.31 (m, 2H).

Example 2 - Preparation of compound 2 in table 1 - 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide

Di-*tert*butyl azodicarboxylate (805 mg, 3.50 mmol) in dichloromethane (5 ml) was slowly added to a mixture of *N*-(2,3-difluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (554 mg, 1.40 mmol), triphenyl phosphine (917 mg, 3.5 mmol) and 3-chloro-1-propanol (172 mg, 1.82 mmol) in dichloromethane (10 ml) and tetrahydrofuran (25 ml) at ambient temperature under argon. The mixture was stirred at ambient temperature for 18 hours and concentrated *in vacuo*. The residual oil was dissolved in dichloromethane and 4.0 N hydrochloric acid in dioxane (2 ml) added. Diethyl ether (10 ml) was added and the resultant precipitate was recovered by filtration, washed with diethyl ether and dried. The solid was dissolved in dichloromethane and treated with an aqueous solution of sodium bicarbonate. The aqueous phase was extracted with dichloromethane (2 x 15 ml) and the combined organic phases were dried and concentrated to yield compound 2 in table 1 (400 mg, 60 % yield):
^{1}H-NMR (DMSO d_6, TFA): 8.98 (s, 1H), 8.62 (d, 1H), 8.41 (s, 1H), 7.98 (s, 1H), 7.75 (t, 1H), 7.56 (d, 1H), 7.28 (s, 1H), 7.21 (m, 2H), 5.26 (s, 2H), 4.32 (t, 2H), 3.85 (t, 2H), 2.30 (t, 2H).

MS (+ve ESI): 473 (M+H)$^+$

N-(2,3-difluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide used as starting material, was obtained as follows:

a) 2-Amino-4-fluorobenzoic acid (7.75 g, 50 mmol) was heated in formamide (50 ml) at 150 °C for 8 hours. Water (50 ml) was added to the reaction mixture and the solid recovered by filtration, washed with water and dried *in vacuo* (50 °C, 0.1 mm Hg) to yield 7-fluoroquinazolin-4-(3H)-one (7.3 g, 89 % yield):
^{1}H-NMR (DMSO d_6): 8.21 (m, 1H), 8.15 (s, 1H), 7.45 (m, 1H), 7.38 (m, 1H).

b) Sodium (10.3 g, 0.45 mol) was added to benzyl alcohol (200 ml, 1.94 mol) under argon and the mixture heated at 120 °C for 4 hours. 7-Fluoroquinazolin-4-(3H)-one (15 g, 90 mmol) was added to the mixture and the reaction heated at 120 °C for 18 hours. The mixture was cooled, poured into water (800 ml) and the pH adjusted to 4 with hydrochloric acid (2 N, 150 ml). The resultant precipitate was collected by filtration, washed with water, pentane and diethyl ether to yield 7-(benzyloxy)quinazolin-4-(3H)-one (22.3 g, 98 % yield):
^{1}H-NMR (DMSO d_6): 8.05 (s, 1H), 8.02 (d, 1H), 7.48 (m, 2H), 7.41 (t, 2H), 7.36 (d, 1H), 7.17 (m, 2H), 5.26 (s, 2H).

c) Dimethylformamide (0.5 ml) was added to a suspension of 7-(benzyloxy)quinazolin-4-(3H)-one (5.04 g, 20 mmol) in thionyl chloride (50 ml) and the mixture heated at reflux for 2 hours. The thionyl chloride was removed *in vacuo* and the residual oil dissolved in dichloromethane (100 ml). This solution was slowly added to an aqueous saturated solution of sodium bicarbonate (100 ml) and the organic phase recovered. The aqueous phase was extracted with dichloromethane (2 x 50 ml) and the combined organics dried and concentrated to yield 7-(benzyloxy)-4-chloroquinazoline (4.68 g, 86.5 % yield):
^{1}H-NMR (DMSO d_6, TFA): 9.15 (s, 1H), 8.15 (d, 1H), 7.51 (m, 2H), 7.43 (m, 2H), 7.38 (m, 2H), 7.30 (m, 1H), 5.32 (s, 2H).

d) 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (504 mg, 2 mmol) was added to a solution of 7-(benzyloxy)-4-chloroquinazoline (541 mg, 2 mmol) in dimethylacetamide (10 ml) under argon. A solution of 4.0 N hydrochloric acid in dioxane (500 μl, 2 mmol) was added and the mixture was heated at 90 °C for 1.5 hours. The mixture

was cooled, diluted with dichloromethane and the resultant precipitate recovered by filtration. The solid was washed with dichloromethane and diethyl ether and dried *in vacuo* to yield 2-(4-{[7-(benzyloxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (850 mg, 81 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.97 (s, 1H), 8.68 (d, 1H), 8.41 (s, 1H), 8.00 (s, 1H), 7.75 (t, 1H), 7.61 (d, 1H), 7.53 (m, 2H), 7.45 (m, 2H), 7.42 (d, 1H), 7.36 (m, 1H), 7.20 (m, 2H), 5.38 (s, 2H), 5.25 (s, 2H).

MS (+ve ESI): 487.1 $(M+H)^+$

e) 2-(4-{[7-(benzyloxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (836 mg, 1.60 mmol) was dissolved in trifluoroacetic acid (8 ml) and heated under reflux for 2.5 hours. The solution was concentrated and the residual oil was dissolved in methanol and neutralised with an aqueous solution of sodium bicarbonate. Water was added to the mixture and the solid recovered by filtration and dried *in vacuo* to yield *N*-(2,3-difluorophenyl)-2-{4-[(7-hydroxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (633 mg, 100 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.92 (s, 1H), 8.51 (d, 1H), 8.36 (s, 1H), 7.92 (s, 1H), 7.70 (t, 1H), 7.32 (d, 1H), 7.21 (m, 2H), 7.13 (s, 1H), 5.22 (s, 2H).

MS (+ve ESI): 397 $(M+H)^+$

2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide, used as starting material was prepared as follows:

a) An analogous reaction to that described in example 1a, but starting 2,3-difluoroaniline (1.55 g, 120 mmol) yielded N-(2,3-difluorophenyl)-2-(4-nitro-1*H*-pyrazol-1-yl)acetamide (1.13 g, 40 % yield):

^{1}H-NMR (DMSO d_6): 10.43 (br s, 1H), 8.90 (s, 1H), 8.30 (s, 1H), 7.69 (m, 1H), 7.19 (m, 2H), 5.23 (s, 2H).

b) An analogous reaction to that described in example 1b, but starting with N-(2,3-difluorophenyl)-2-(4-nitro-1*H*-pyrazol-1-yl)acetamide (5.22 g, 185 mmol) yielded 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (4.2 g, 90 % yield):

^{1}H-NMR (DMSO d_6): 7.68 (m, 1H), 7.17 (m, 2H), 7.09 (s, 1H), 6.97 (s, 1H), 4.90 (s, 2H), 3.85 (br s, 2H).

MS (+ve ESI) : 253 (M+H)$^+$

Example 3 - Preparation of compound 3 in table 1 - 2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide

4 N hydrochloric acid in dioxane (250 μl, 1 mmol) was added to a solution of 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (293 mg, 1 mmol) and 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline (287 mg, 1 mmol) in dimethylacetamide (8 ml) and the mixture heated under argon at 90 °C for 1 hour. The reaction was cooled, diluted with dichloromethane (20 ml) and the resultant precipitate recovered by filtration. The solid was washed with dichloromethane, diethyl ether and dried *in vacuo* to yield compound 3 in table 1 (480 mg, 90 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.94 (s, 1H), 8.41 (s, 1H), 8.13 (s, 1H), 7.98 (s, 1H), 7.74 (m, 1H), 7.34 (s, 1H), 7.21 (m, 2H), 5.24 (s, 2H), 4.33 (t, 2H), 4.03 (s, 3H), 3.83 (t, 2H), 2.32 (t, 2H).

MS (+ve ESI): 503 (M+H)$^+$

Example 4 - Preparation of compound 4 in table 1 - 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 3 but starting with 2-(4-amino-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (312 mg, 1.34 mmol) and 4-chloro-7-(3-chloropropoxy)quinazoline (344 mg, 1.34 mmol) yielded compound 4 in table 1 (624 mg, 95 % yield):

^{1}H-NMR (DMSO d_6): 11.84 (s, 1H), 10.81 (s, 1H), 8.94 (s, 1H), 8.82 (m, 1H), 8.42 (s, 1H), 8.02 (s, 1H), 7.60 (m, 1H), 7.49 (m, 1H), 7.36 (m, 3H), 6.92 (m, 1H), 5.15 (s, 2H), 4.13 (t, 2H), 3.85 (t, 2H), 2.28 (t, 2H).

MS (+ve ESI) : 455 (M+H)$^+$

4-chloro-7-(3-chloropropoxy)quinazoline, used as the starting material was obtained as follows:

a) Formamidine acetate (20.13 g, 193.4 mmol) was added to a solution of 2-amino-4-fluorobenzoic acid (15 g, 96.7 mmol) in 2-methoxyethanol (97 ml) and the mixture heated to reflux for 18 hours. The reaction was cooled, concentrated and the residue stirred in aqueous ammonium hydroxide (0.01 M, 250 ml) for 1 hour. The suspension was filtered, washed with

water and dried over phosphorus pentoxide to yield 7-fluoroquinazolin-4-ol as an off-white solid (10.35 g, 65 % yield):

^{1}H-NMR (DMSO d_6): 12.32 (br s, 1H), 8.19 (dd, 1H), 8.14 (s, 1H), 7.45 (m, 1H), 7.39 (m, 1H).

^{19}F-NMR (DMSO d_6): -105 (m)

MS (-ve ESI): 163 $(M-H)^-$,

MS (+ve ESI): 165 $(M+H)^+$

b) Sodium hydride (14.6 g, 365 mmol) was added at 0 °C to a solution of 1,3-propanediol (27.8 g, 365 mmol) in dimethylformamide (70 ml). 7-Fluoroquinazolin-4-ol (10 g, 60.9 mmol) was added portion wise and the reaction mixture heated at 60 °C, then at 110 °C for 3 hours. The reaction was cooled to 0 °C, quenched with water (280 ml) and adjusted to pH 5.9. The resulting suspension was filtered, washed with water then diethyl ether and dried over phosphorus pentoxide to yield 7-(3-hydroxypropoxy)quinazolin-4-ol as a white powder (12.41 g, 92 % yield):

^{1}H-NMR (DMSO d_6): 11.90 (br s, 1H), 8.04 (s, 1H), 8.00 (d, 1H), 7.10 (m, 2H), 4.17 (t, 2H), 3.58 (t, 2H), 1.92 (m, 2H).

MS (+ve ESI): 221 $(M+H)^+$

c) Dimethylformamide (1 ml) was added to a mixture of 7-(3-hydroxypropoxy)quinazolin-4-ol (10.5 g, 47.7 mmol) and thionyl chloride (100 ml, 137 mmol) and the reaction mixture heated to 85 °C for 1 hour. The mixture was cooled to ambient temperature, diluted with toluene and evaporated to dryness. This was repeated until all thionyl chloride was removed. The residue was dissolved in dichloromethane and washed with a saturated sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane and the combined organics were dried (magnesium sulphate) and concentrated to leave a yellow solid. Trituration with diethyl ether removed a less soluble impurity and the diethyl ether filtrate was concentrated to yield 4-chloro-7-(3-chloropropoxy)quinazoline as an off-white solid (8.5 g, 70 % yield):

^{1}H-NMR (DMSO d_6): 13.25 (br s, 1H), 8.34 (s, 1H), 8.06 (d, 1H), 7.17 (m, 2H), 4.21 (t, 2H), 3.83 (t, 2H), 2.23 (m, 2H).

MS (+ve ESI): 257, 259 $(M+H)^+$

Example 5 - Preparation of compound 5 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

(2S)-Pyrrolidin-2-ylmethanol (80 mg, 0.8 mmol) was added to a solution of 2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (104 mg, 0.2 mmol) and potassium iodide (66 mg, 0.4 mmol) in dimethylacetamide (0.5 ml) and the mixture heated under argon at 90 °C for 3 hours. The solvent was evaporated, and the residue purified by preparative LCMS (Waters symmetry 5 μm column, 19 x 100 mm) to yield compound 5 in table 2 (100 mg, 91 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.97 (s, 1H), 8.41 (s, 1H), 8.09 (s, 1H), 7.96 (s, 1H), 7.61 (d, 1H), 7.34 (m, 3H), 6.91 (t, 1H), 5.15 (s, 2H), 4.30 (t, 2H), 4.03 (s, 3H), 3.78 (m, 1H), 3.62 (m, 4H), 3.25 (m, 2H), 2.38 (m, 2H), 2.14 (m, 1H), 2.05 (m, 1H), 1.91 (m, 1H), 1.81 (m, 1H).

MS (+ve ESI): 550.3 $(M+H)^+$

Example 6 - Preparation of compound 6 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with 2-(isobutyl amino)ethanol (94 mg, 0.8 mmol) yielded compound 6 in table 2 (75 mg, 66 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.98 (s, 1H), 8.42 (s, 1H), 8.09 (s, 1H), 7.95 (s, 1H), 7.61 (d, 1H), 7.36 (m, 3H), 6.92 (t, 1H), 5.15 (s, 2H), 4.30 (m, 2H), 4.03 (s, 3H), 3.80 (m, 2H), 3.38 (m, 2H), 3.29 (m, 2H), 3.12 (m, 1H), 3.08 (m, 1H), 2.31 (m, 2H), 1.10 (t, 1H), 1.01 (d, 6H).

MS (+ve ESI): 566.2 $(M+H)^+$

Example 7 - Preparation of compound 7 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with 2-(propylamino)ethanol (82 mg, 0.8 mmol) yielded compound 7 in table 2 (85 mg, 77 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.97 (s, 1H), 8.39 (s, 1H), 8.08 (s, 1H), 7.95 (s, 1H), 7.60 (m, 1H), 7.38 (m, 1H), 7.32 (m, 2H), 6.92 (m, 1H), 5.15 (s, 2H), 4.29 (t, 2H), 4.02 (s, 3H), 3.77 (t, 2H), 3.39 (m, 2H), 3.28 (t, 2H), 3.15 (m, 2H), 2.28 (m, 2H), 1.71 (m, 2H), 0.95 (t, 3H).

MS (+ve ESI): 552.2 $(M+H)^+$

Example 8 - Preparation of compound 8 in table 2 - *N*-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-piperidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 5 but starting with piperidine (55 mg, 0.65 mmol) yielded compound 8 in table 2 (78 mg, 73 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.37 (m, 1H), 7.34 (m, 1H), 7.31 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.41 (t, 2H), 2.35 (m, 4H), 1.94 (m, 2H), 1.51 (m, 4H), 1.39 (m, 2H).

MS (+ve ESI): 534.2 $(M+H)^+$

Example 9 - Preparation of compound 9 in table 2 - *N*-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 5 but stating with pyrrolidine (46 mg, 0.65 mmol) yielded compound 9 in table 2 (71 mg, 69 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.42 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.59 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.83 (m, 1H), 5.06 (s, 2H), 4.17 (t, 2H), 3.96 (s, 3H), 2.54 (t, 2H), 2.45 (m, 4H), 1.96 (m, 2H), 1.69 (m, 4H).

MS (+ve ESI): 520.2 $(M+H)^+$

Example 10 - Preparation of compound 10 in table 2 - 2-[4-({7-[3-(diethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with diethyl amine (48 mg, 0.65 mmol) yielded compound 10 in table 2 (62 mg, 59 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.81 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.52 (t, 2H), 2.46 (m, 4H), 1.89 (m, 2H), 0.95 (t, 6H).

MS (+ve ESI): 522.1 $(M+H)^+$

Example 11 - Preparation of compound 11 in table 2 - *N*-(3-fluorophenyl)-2-(4-{[6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 5 but starting with piperazine (56 mg, 0.65 mmol) yielded compound 11 in table 2 (54 mg, 51 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.58 (m, 1H), 7.39 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.69 (m, 4H), 2.41 (t, 2H), 2.31 (m, 4H), 1.94 (m, 2H).

MS (+ve ESI): 535.1 $(M+H)^+$

Example 12 - Preparation of compound 12 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting 2-(methylamino)ethanol (49 mg, 0.65 mmol) yielded compound 12 in table 2 (67 mg, 64 % yield):

^{1}H-NMR (DMSO d_6): 9.18 (s, 1H), 8.42 (s, 1H), 8.35 (s, 1H), 7.81 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.16 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.36 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.47 (m, 2H), 2.5 (m, 2H), 2.42 (t, 2H), 2.2 (s, 3H), 1.92 (m, 2H).

MS (+ve ESI): 524.1 $(M+H)^+$

Example 13 - Preparation of compound 13 in table 2 - 2-[4-({7-[3-(cyclopropylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with cyclopropylamine (37 mg, 0.65 mmol) yielded compound 13 in table 2 (51 mg, 51 % yield):

^{1}H-NMR (DMSO d_6): 9.71 (s, 1H), 8.50 (s, 1H), 8.37 (s, 1H), 7.80 (s, 1H), 7.78 (s, 1H), 7.61 (m, 1H), 7.39 (m, 1H), 7.34 (m, 1H), 7.18 (s, 1H), 6.95 (m, 1H), 5.09 (s, 2H), 4.19 (t, 2H), 3.98 (s, 3H), 2.77 (t, 2H), 2.09 (m, 1H), 1.94 (m, 2H), 0.37 (m, 2H), 0.23 (m, 2H).

MS (+ve ESI): 506.1 $(M+H)^+$

Example 14 - Preparation of compound 14 in table 2 - 2-{4-[(7-{3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with N,N,N'-trimethylethane-1,2-diamine (66 mg, 0.65 mmol) yielded compound 14 in table 2 (49 mg, 45 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.37 (m, 1H), 7.31 (m, 1H), 7.14 (s, 1H), 6.93 (m, 1H), 5.06 (s, 2H), 4.15 (t, 2H), 3.96 (s, 3H), 2.50 (m, 2H), 2.41 (m, 2H), 2.29 (m, 2H), 2.19 (s, 3H), 2.11 (s, 6H), 1.91 (m, 2H).

MS (+ve ESI): 551.1 $(M+H)^+$

Example 15 - Preparation of compound 15 in table 2 - *N*-(3-fluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 5 but starting with 1-methylpiperazine (65 mg, 0.65 mmol) yielded compound 15 in table 2 (80 mg, 73 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.90 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.44 (t, 2H), 2.11-2.60 (m, 8H), 2.14 (s, 3H), 1.94 (m, 2H).

MS (+ve ESI): 549.1 $(M+H)^+$

Example 16 - Preparation of compound 16 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with (2R)-pyrrolidin-2-ylmethanol (66 mg, 0.65 mmol) yielded compound 16 in table 2 (74 mg, 67 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.31 (m, 1H), 7.16 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.34 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.17 (m, 1H), 3.07 (m, 1H), 2.96 (m, 1H), 2.41 (m, 3H), 2.15 (m, 1H), 1.94 (m, 2H), 1.80 (m, 1H), 1.65 (m, 2H), 1.56 (m, 1H).

MS (+ve ESI): 550.1 $(M+H)^+$

Example 17 - Preparation of compound 17 in table 2 - *N*-(3-fluorophenyl)-2-[4-({7-[3-(4-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 5 but starting with 4-piperidinol (66 mg, 0.65 mmol) yielded compound 17 in table 2 (110 mg, 100 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.97 (s, 1H), 8.48 (s, 1H), 8.14 (s, 1H), 7.98 (s, 1H), 7.61 (m, 1H), 7.38 (m, 2H), 7.36 (s, 1H), 6.91 (m, 1H), 5.16 (s, 2H), 4.31 (t, 2H), 4.04 (s, 3H), 3.70 (m, 1H), 3.57 (d, 1H), 3.41 (d, 1H), 3.30 (m, 3H), 3.04 (t, 1H), 2.32 (m, 2H), 2.02 (m, 1H), 1.89 (m, 2H), 1.61 (m, 1H).

MS (+ve ESI): 550.1 $(M+H)^+$

Example 18 - Preparation of compound 18 in table 2 - 2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with 2,2'-iminodiethanol (68 mg, 0.65 mmol) yielded compound 18 in table 2 (53 mg, 48 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.17 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.35 (t, 2H), 4.18 (t, 2H), 3.96 (s, 3H), 3.42 (m, 4H), 2.64 (m, 2H), 2.54 (m, 4H), 1.90 (m, 2H).

MS (+ve ESI): 554.2 $(M+H)^+$

Example 19 - Preparation of compound 19 in table 2 - 2-{4-[(7-{3-[ethyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with ethyl (methyl)amine (38 mg, 0.65 mmol) yielded compound 19 in table 2 (67 mg, 66 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.31 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.46 (t, 2H), 2.36 (q, 2H), 2.16 (s, 3H), 1.92 (m, 2H), 0.98 (t, 3H).

MS (+ve ESI): 508.1 $(M+H)^+$

Example 20 - Preparation of compound 20 in table 2 - 2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with 2-(ethylamino)ethanol (58 mg, 0.65 mmol) yielded compound 20 in table 2 (63 mg, 58 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.33 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.42 (m, 2H), 2.61 (t, 2H), 2.50 (m, 4H), 1.89 (m, 2H), 0.96 (t, 3H).
MS (+ve ESI): 538.1 $(M+H)^+$

Example 21 - Preparation of compound 21 in table 2 - 2-{4-[(7-{3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with N'-ethyl-N,N-dimethylethane-1,2-diamine (76 mg, 0.65 mmol) yielded compound 21 in table 2 (33 mg, 29 % yield):
^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 2.57 (t, 2H), 2.48 (m, 4H), 2.27 (t, 2H), 2.09 (s, 6H), 1.88 (m, 2H), 0.95 (t, 3H).
MS (+ve ESI): 565.1 $(M+H)^+$

Example 22 - Preparation of compound 22 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with 2-piperidin-2-ylethanol (84 mg, 0.65 mmol) yielded compound 22 in table 2 (67 mg, 58 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.38 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.44 (m, 2H), 2.76 (m, 2H), 2.46 (m, 2H), 2.23 (m, 1H), 1.91 (m, 2H), 1.74 (m, 1H), 1.59 (m, 2H), 1.46 (m, 3H), 1.28 (m, 2H).
MS (+ve ESI): 578.2 $(M+H)^+$

Example 23 - Preparation of compound 23 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with 2-piperazin-1-ylethanol (85 mg, 0.65 mmol) yielded compound 23 in table 2 (85 mg, 74 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.36 (t, 1H), 4.16 (t, 2H), 3.96 (s, 3H), 3.47 (m, 2H), 2.35-2.45 (m, 12H), 1.94 (m, 2H).

MS (+ve ESI): 579.2 $(M+H)^+$

Example 24 - Preparation of compound 24 in table 2 - 2-{4-[(7-{3-[(cyclopropylmethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with (cyclopropylmethyl)amine (46 mg, 0.65 mmol) yielded compound 24 in table 2 (53 mg, 51 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.16 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.19 (t, 2H), 3.96 (s, 3H), 2.71 (t, 2H), 2.39 (d, 2H), 1.93 (m, 2H), 0.88 (m, 1H), 0.39 (m, 2H), 0.11 (m, 2H).

MS (+ve ESI): 520.1 $(M+H)^+$

Example 25 - Preparation of compound 25 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with 2-piperidin-4-ylethanol (84 mg, 0.65 mmol) yielded compound 25 in table 2 (101 mg, 88 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.32 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.43 (m, 2H), 2.85 (m, 2H), 2.42 (t, 2H), 1.94 (m, 2H), 1.85 (t, 2H), 1.61 (d, 2H), 1.35 (t, 3H), 1.13 (m, 2H).

MS (+ve ESI): 578.1 $(M+H)^+$

Example 26 - Preparation of compound 26 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(prop-2-yn-1-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with N-methylprop-2-yn-1-amine (45 mg, 0.65 mmol) yielded compound 26 in table 2 (58 mg, 56 % yield):

^{1}H-NMR (DMSO d_6): 8.61 (s, 1H), 8.37 (s, 1H), 7.99 (s, 1H), 7.86 (s, 1H), 7.61 (m, 1H), 7.37 (m, 1H), 7.33 (m, 1H), 7.23 (s, 1H), 6.92 (m, 1H), 5.09 (s, 2H), 4.24 (t, 2H), 3.99 (s, 3H), 3.71 (m, 1H), 3.08 (m, 2H), 2.74 (m, 2H), 2.17 (m, 2H).

MS (+ve ESI): 518.1 $(M+H)^+$

Example 27 - Preparation of compound 27 in table 2 - 2-{4-[(7-{3-[allyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with N-methylprop-2-en-1-amine (46 mg, 0.65 mmol) yielded compound 27 in table 2 (79 mg, 76 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.83 (m, 1H), 5.18 (d, 1H), 5.07 (d, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.98 (d, 2H), 2.48 (m, 2H), 2.16 (s, 3H), 1.94 (m, 2H).

MS (+ve ESI): 520.1 $(M+H)^+$

Example 28 - Preparation of compound 28 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[isobutyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with isobutyl(methyl)amine (57 mg, 0.65 mmol) yielded compound 28 in table 2 (64 mg, 60 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.13 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.17 (t, 2H), 3.96 (s, 3H), 2.45 (t, 2H), 2.15 (s, 3H), 2.04 (d, 2H), 1.92 (m, 2H), 1.72 (m, 1H), 0.82 (d, 6H).

MS (+ve ESI): 536.2 $(M+H)^+$

Example 29 - Preparation of compound 29 in table 2 - *N*-(3-fluorophenyl)-2-[4-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 5 but starting with piperidin-3-ol (66 mg, 0.65 mmol) yielded compound 29 in table 2 (78 mg, 71 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.16 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.59 (d, 1H), 4.16 (t, 2H), 3.96 (s, 3H), 3.48 (m, 2H), 2.83 (m, 1H), 2.67 (m, 1H), 2.46 (m, 2H), 1.94 (m, 2H), 1.85 (m, 1H), 1.76 (m, 2H), 1.61 (m, 1H), 1.42 (m, 1H).

MS (+ve ESI): 550.1 $(M+H)^+$

Example 30 - Preparation of compound 30 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with piperidin-4-ylmethanol (75 mg, 0.65 mmol) yielded compound 30 in table 2 (88 mg, 78 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.40 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.23 (m, 2H), 2.87 (d, 2H), 2.43 (t, 2H), 1.94 (m, 2H), 1.85 (t, 2H), 1.63 (d, 2H), 1.33 (m, 1H), 1.13 (m, 2H).

MS (+ve ESI): 564.2 $(M+H)^+$

Example 31 - Preparation of compound 31 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with methyl(propyl)amine (48 mg, 0.65 mmol) yielded compound 31 in table 2 (68 mg, 66 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.46 (t, 2H), 2.26 (t, 2H), 2.16 (s, 3H), 1.92 (m, 2H), 1.42 (m, 2H), 0.83 (t, 3H).

MS (+ve ESI): 522.1 $(M+H)^+$

Example 32 - Preparation of compound 32 in table 2 - 2-{4-[(7-{3-[(cyclopropylmethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with (cyclopropylmethyl)propylamine (74 mg, 0.65 mmol) yielded compound 32 in table 2 (3 mg, 3 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.18 (t, 2H), 3.95 (s, 3H), 2.64 (m, 2H), 2.43 (m, 2H), 2.31 (d, 2H), 1.90 (m, 2H), 1.42 (m, 2H), 0.83 (m, 4H), 0.40 (m, 2H), 0.06 (m, 2H).

MS (+ve ESI): 562.2 $(M+H)^+$

Example 33 - Preparation of compound 33 in table 2 - 2-{4-[(7-{3-[[2-(diethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with N,N-diethyl-N'-methylethane-1,2-diamine (85 mg, 0.65 mmol) yielded compound 33 in table 2 (83 mg, 71 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.41 (m, 10H), 2.19 (s, 3H), 1.91 (m, 2H), 0.90 (t, 6H).

MS (+ve ESI): 579.2 $(M+H)^+$

Example 34 - Preparation of compound 34 in table 2 - 2-{4-[(7-{3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with N,N,N'-triethylethane-1,2-diamine (94 mg, 0.65 mmol) yielded compound 34 in table 2 (70 mg, 59 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.17 (t, 2H), 3.96 (s, 3H), 2.58 (m, 2H), 2.42 (m, 10H), 1.88 (m, 2H), 0.96 (t, 3H), 0.91 (t, 6H).

MS (+ve ESI): 593.2 $(M+H)^+$

Example 35 - Preparation of compound 35 in table 2 - *N*-(3-fluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 5 but starting with 1-methyl-1,4-diazepane (74 mg, 0.65 mmol) yielded compound 35 in table 2 (55 mg, 49 % yield):
^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.95 (s, 3H), 2.63 (m, 10H), 2.23 (s, 3H), 1.91 (m, 2H), 1.71 (m, 2H).
MS (+ve ESI): 563.2 $(M+H)^+$

Example 36 - Preparation of compound 36 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with 2-(isopropylamino)ethanol (67 mg, 0.65 mmol) yielded compound 36 in table 2 (82 mg, 74 % yield):
^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.27 (t, 1H), 4.16 (t, 2H), 3.97 (s, 3H), 3.35 (m, 2H), 2.89 (m, 1H), 2.54 (m, 2H), 2.45 (m, 2H), 1.86 (m, 2H), 0.92 (d, 6H).
MS (+ve ESI): 552.2 $(M+H)^+$

Example 37 - Preparation of compound 37 in table 2 - 2-{4-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with 2-(cyclopropylamino)ethanol (66 mg, 0.65 mmol) yielded compound 37 in table 2 (73 mg, 66 % yield):
^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.32 (m, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.5 (m, 2H), 2.76 (t, 2H), 2.65 (t, 2H), 1.95 (m, 2H), 1.82 (m, 1H), 0.43 (m, 2H), 0.31 (m, 2H).

MS (+ve ESI): 550.1 $(M+H)^+$

Example 38 - Preparation of compound 38 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with 2-((2-methoxyethyl)amino)ethanol (77 mg, 0.65 mmol) yielded compound 38 in table 2 (97 mg, 85 % yield):

^{1}H-NMR (DMSO d$_6$): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.31 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.43 (m, 2H), 3.37 (m, 2H), 3.20 (s, 3H), 2.64 (m, 4H), 2.53 (t, 2H), 1.91 (m, 2H).

MS (+ve ESI): 568.1 $(M+H)^+$

Example 39 - Preparation of compound 39 in table 2 - 2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with 2-(cyclobutylamino)ethanol (75 mg, 0.65 mmol) yielded compound 39 in table 2 (106 mg, 94 % yield):

^{1}H-NMR (DMSO d$_6$): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.53 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.35 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.42 (m, 2H), 3.12 (m, 1H), 2.56 (t, 2H), 2.46 (t, 2H), 1.94 (m, 2H), 1.88 (m, 2H), 1.75 (m, 2H), 1.54 (m, 2H).

MS (+ve ESI): 564.1 $(M+H)^+$

Example 40 - Preparation of compound 40 in table 2 - 2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with 2-((cyclopropylmethyl)amino)ethanol (75 mg, 0.65 mmol) yielded compound 40 in table 2 (75 mg, 66 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 3H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.32 (t, 1H), 4.18 (t, 2H), 3.96 (s, 3H), 3.46 (m, 2H), 2.69 (t, 2H), 2.58 (t, 2H), 2.35 (d, 2H), 1.91 (m, 2H), 0.83 (m, 1H), 0.41 (m, 2H), 0.08 (m, 2H).

MS (+ve ESI): 564.1 $(M+H)^+$

Example 41 - Preparation of compound 41 in table 2 - 2-{4-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with 2-((cyclobutylmethyl)amino)ethanol (84 mg, 0.65 mmol) yielded compound 41 in table 2 (90 mg, 78 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.07 (s, 2H), 4.29 (t, 1H), 4.15 (t, 2H), 3.97 (s, 3H), 3.42 (m, 2H), 2.57 (t, 2H), 2.47 (m, 4H), 1.93 (m, 3H), 1.89 (t, 2H), 1.76 (m, 2H), 1.59 (m, 2H).

MS (+ve ESI): 578.2 $(M+H)^+$

Example 42 - Preparation of compound 42 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with 2-(prop-2-yn-1-ylamino)ethanol (64 mg, 0.65 mmol) yielded compound 42 in table 2 (69 mg, 63 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.38 (m, 1H), 7.32 (m, 1H), 7.16 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.43 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.46 (m, 2H), 3.41 (d, 2H), 3.09 (t, 1H), 2.63 (t, 2H), 2.54 (t, 2H), 1.92 (m, 2H).

MS (+ve ESI): 548.1 $(M+H)^+$

Example 43 - Preparation of compound 43 in table 2 - 2-{4-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with 2-(allylamino)ethanol (66 mg, 0.65 mmol) yielded compound 43 in table 2 (100 mg, 91 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.83 (m, 1H), 5.18 (dd, 1H), 5.09 (dd, 1H), 5.06 (s, 2H), 4.36 (t, 1H), 4.16 (t, 2H), 3.96 (s, 3H), 3.45 (m, 1H), 3.11 (d, 2H), 2.61 (t, 2H), 1.92 (m, 2H).

MS (+ve ESI): 550.1 $(M+H)^+$

Example 44 - Preparation of compound 44 in table 2 - 2-{4-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with 2-((2,2-dimethylpropyl)amino)ethanol (85 mg, 0.65 mmol) yielded compound 44 in table 2 (85 mg, 66 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.33 (t, 1H), 4.17 (t, 2H), 3.95 (s, 3H), 3.44 (m, 2H), 2.64 (t, 2H), 2.54 (t, 2H), 2.21 (s, 2H), 1.91 (m, 2H), 0.83 (s, 9H).

MS (+ve ESI): 580.2 $(M+H)^+$

Example 45 - Preparation of compound 45 in table 2 - *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with 2-((3,3,3-trifluoropropyl)amino)ethanol (102 mg, 0.65 mmol) yielded compound 45 in table 2 (80 mg, 66 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.16 (s, 1H), 6.92 (m, 1H), 5.07 (s, 2H), 4.41 (m, 1H),

4.17 (t, 2H), 3.96 (s, 3H), 3.45 (t, 2H), 2.72 (t, 2H), 2.63 (t, 2H), 2.53 (m, 2H), 2.40 (m, 2H), 1.92 (m, 2H).

MS (+ve ESI): 606.3 $(M+H)^+$

Example 46 - Preparation of compound 46 in table 2 - 2-(4-{[7-(3-azetidin-1-ylpropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 5 but starting with azetidine (37 mg, 0.65 mmol) yielded compound 46 in table 2 (13 mg, 13 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.14 (s, 1H), 6.91 (m, 1H), 5.06 (s, 2H), 4.13 (m, 2H), 3.95 (s, 3H), 3.09 (t, 4H), 2.51 (m, 2H), 1.95 (m, 2H), 1.76 (m, 2H).

MS (+ve ESI): 506.1 $(M+H)^+$

Example 47 - Preparation of compound 47 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 5 but starting with 2-(4-{[7-(3-chloropropoxy)-6-methoxyquinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (129 mg, 0.23 mmol) and 2-(isobutylamino)ethanol (146 mg, 0.93 mmol) yielded compound 47 in table 3 (95 mg, 70 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.74 (m, 3H), 7.21 (m, 2H), 7.14 (s, 1H), 5.17 (s, 2H), 4.30 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.43 (m, 2H), 2.58 (m, 2H), 2.47 (m, 2H), 2.15 (m, 2H), 1.89 (m, 2H), 1.67 (m, 1H), 0.81 (d, 6H).

MS (+ve ESI): 584.2 $(M+H)^+$

Example 48 - Preparation of compound 48 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with (2S)-pyrrolidin-2-ylmethanol (98 μl, 1 mmol) yielded compound 48 in table 3 (105 mg, 74 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.74 (m, 3H), 7.21 (m, 2H), 7.16 (s, 1H), 5.16 (s, 2H), 4.33 (t, 1H), 4.17 (t, 2H), 3.95 (s, 3H), 3.39 (m, 1H), 3.18 (m, 1H),

3.08 (m, 1H), 2.97 (m, 1H), 2.42 (m, 2H), 2.15 (m, 1H), 1.95 (m, 2H), 1.79 (m, 1H), 1.65 (m, 2H), 1.55 (m, 1H).

MS (+ve ESI): 568.1 $(M+H)^+$

Example 49 - Preparation of compound 49 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with 2-(propylamino)ethanol (82 mg, 0.8 mmol) yielded compound 49 in table 3 (88 mg, 77 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.97 (s, 1H), 8.39 (s, 1H), 8.08 (s, 1H), 7.95 (s, 1H), 7.74 (m, 1H), 7.33 (s, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.29 (t, 2H), 4.02 (s, 3H), 3.77 (t, 2H), 3.33 (m, 2H), 3.28 (m, 2H), 3.15 (m, 2H), 2.28 (m, 2H), 1.71 (m, 2H), 0.95 (t, 3H).

MS (+ve ESI): 570.3 $(M+H)^+$

Example 50 - Preparation of compound 50 in table 3 - *N*-(2,3-difluorophenyl)-2-[4-({7-[3-(dimethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 47 but starting with dimethylamine (29 mg, 0.65 mmol) yielded compound 50 in table 3 (51 mg, 56 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.15 (t, 2H), 3.96 (s, 3H), 2.38 (t, 2H), 2.16 (s, 6H), 1.93 (m, 2H).

MS (+ve ESI): 512.1 $(M+H)^+$

Example 51 - Preparation of compound 51 in table 3 - *N*-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-piperidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 47 but starting with piperidine (55 mg, 0.65 mmol) yielded compound 51 in table 3 (68 mg, 69 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.45 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.73 (m, 1H), 7.19 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.15 (t, 2H), 3.95 (s, 3H), 2.41 (t, 2H), 2.35 (m, 4H), 1.93 (m, 2H), 1.51 (m, 4H), 1.39 (m, 2H).

MS (+ve ESI): 552.2 $(M+H)^+$

Example 52 - Preparation of compound 52 in table 3 - *N*-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 47 but starting with pyrrolidine (46 mg, 0.65 mmol) yielded compound 52 in table 3 (65 mg, 67 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.17 (t, 2H), 3.96 (s, 3H), 2.52 (t, 2H), 2.45 (m, 4H), 1.96 (m, 2H), 1.69 (m, 4H).

MS (+ve ESI): 538.1 $(M+H)^+$

Example 53 - Preparation of compound 53 in table 3 - *N*-(2,3-difluorophenyl)-2-(4-{[6-methoxy-7-(3-piperazin-1-ylpropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)acetamide

An analogous reaction to that described in example 47 but starting with piperazine (56 mg, 0.65 mmol) yielded compound 53 in table 3 (67 mg, 68 % yield):

^{1}H-NMR (DMSO d_6): 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.95 (s, 3H), 2.69 (m, 4H), 2.41 (t, 2H), 2.31 (m, 4H), 1.94 (m, 2H).

MS (+ve ESI): 553.1 $(M+H)^+$

Example 54 - Preparation of compound 54 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with 2-(methylamino)ethanol (49 mg, 0.65 mmol) yielded compound 54 in table 3 (66 mg, 67 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.16 (s, 1H), 5.16 (s, 2H), 4.36 (t, 1H), 4.16 (t, 2H), 3.96 (s, 3H), 3.46 (m, 2H), 2.51 (m, 2H), 2.42 (m, 2H), 2.20 (s, 3H), 1.91 (m, 2H).

MS (+ve ESI): 542.1 $(M+H)^+$

Example 55 - Preparation of compound 55 in table 3 - 2-[4-({7-[3-(cyclopropylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 47 but starting with cyclopropylamine (37 mg, 0.65 mmol) yielded compound 55 in table 3 (67 mg, 71 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.16 (s, 1H), 5.16 (s, 2H), 4.18 (t, 2H), 3.96 (s, 3H), 2.74 (m, 2H), 2.07 (m, 1H), 1.92 (m, 2H), 0.35 (m, 2H), 0.21 (m, 2H).

MS (+ve ESI): 524.1 $(M+H)^+$

Example 56 - Preparation of compound 56 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[[2-(dimethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with N,N,N'-trimethylethane-1,2-diamine (66 mg, 0.65 mmol) yielded compound 56 in table 3 (43 mg, 42 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.49 (m, 2H), 2.40 (m, 2H), 2.29 (m, 2H), 2.19 (s, 3H), 2.11 (s, 6H), 1.91 (m, 2H).

MS (+ve ESI): 569.2 $(M+H)^+$

Example 57 - Preparation of compound 57 in table 3 - *N*-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 47 but starting with 1-methylpiperazine (65 mg, 0.65 mmol) yielded compound 57 in table 3 (85 mg, 84 % yield):

^{1}H-NMR (DMSO d_6): 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.15 (t, 2H), 3.95 (s, 3H), 2.44 (t, 2H), 2.32 (m, 8H), 2.14 (s, 3H), 1.94 (m, 2H).

MS (+ve ESI): 567.2 $(M+H)^+$

Example 58 - Preparation of compound 58 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with (2R)pyrrolidin-2-ylmethanol (66 mg, 0.65 mmol) yielded compound 58 in table 3 (80 mg, 78 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.16 (s, 1H), 5.16 (s, 2H), 4.33 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.38 (m, 1H), 3.17 (m, 1H), 3.07 (m, 1H), 2.96 (m, 1H), 2.41 (m, 2H), 2.14 (m, 1H), 1.94 (m, 2H), 1.79 (m, 1H), 1.65 (m, 2H), 1.55 (m, 1H).

MS (+ve ESI): 568.1 $(M+H)^+$

Example 59 - Preparation of compound 59 in table 3 - *N*-(2,3-difluorophenyl)-2-[4-({7-[3-(4-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 47 but starting with piperidin-4-ol (66 mg, 0.65 mmol) yielded compound 59 in table 3 (102 mg, 100 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.54 (m, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.44 (m, 1H), 2.73 (m, 2H), 2.43 (m, 2H), 2.02 (m, 2H), 1.92 (m, 2H), 1.71 (m, 2H), 1.39 (m, 2H).

MS (+ve ESI): 568.2 $(M+H)^+$

Example 60 - Preparation of compound 60 in table 3 - 2-{4-[(7-{3-[bis(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 47 but starting with 2,2'-iminodiethanol (68 mg, 0.65 mmol) yielded compound 60 in table 3 (95 mg, 93 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.72 (m, 1H), 7.21 (m, 2H), 7.17 (s, 1H), 5.16 (s, 2H), 4.34 (t, 2H), 4.18 (t, 2H), 3.96 (s, 3H), 3.41 (m, 4H), 2.52 (m, 4H), 2.63 (m, 2H), 1.91 (m, 2H).

MS (+ve ESI): 572.1 $(M+H)^+$

Example 61 - Preparation of compound 61 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with ethyl(methyl)amine (38 mg, 0.65 mmol) yielded compound 61 in table 3 (58 mg, 61 % yield): ^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.72 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.46 (m, 2H), 2.36 (q, 2H), 2.16 (s, 3H), 1.92 (m, 2H), 0.98 (t, 3H).

MS (+ve ESI): 526.1 (M+H)$^+$

Example 62 - Preparation of compound 62 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with 2-(ethylamino)ethanol (58 mg, 0.65 mmol) yielded compound 62 in table 3 (91 mg, 91 % yield): ^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.72 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.32 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.43 (m, 2H), 2.59 (t, 2H), 2.50 (m, 2H), 1.89 (m, 2H), 0.95 (t, 3H).

MS (+ve ESI): 556.1 (M+H)$^+$

Example 63 - Preparation of compound 63 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[[2-(dimethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with N'-ethyl-N,N-dimethylethane-1,2-diamine (76 mg, 0.65 mmol) yielded compound 63 in table 3 (29 mg, 27 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.42 (s, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.77 (m, 1H), 7.40 (s, 1H), 7.21 (m, 2H), 5.27 (s, 2H), 4.31 (m, 2H), 4.04 (s, 3H), 3.66 (m, 2H), 3.60 (m, 2H), 3.51 (m, 2H), 3.23 (s, 6H), 3.08 (m, 2H), 2.42 (m, 2H), 1.26 (t, 3H).

MS (+ve ESI): 583.2 (M+H)$^+$

Example 64 - Preparation of compound 64 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[2-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with 2-piperidin-2-ylethanol (84 mg, 0.65 mmol) yielded compound 64 in table 3 (86 mg, 80 % yield):
^{1}H-NMR (DMSO d$_6$): 9.68 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.38 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.44 (m, 2H), 2.76 (m, 2H), 2.44 (m, 2H), 2.23 (m, 1H), 1.91 (m, 2H), 1.73 (m, 1H), 1.58 (m, 2H), 1.46 (m, 3H), 1.28 (m, 2H).
MS (+ve ESI): 596.2 (M+H)$^+$

Example 65 - Preparation of compound 65 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with 2-piperazine-1-ylethanol (85 mg, 0.65 mmol) yielded compound 65 in table 3 (75 mg, 70 % yield):
^{1}H-NMR (DMSO d$_6$): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.77 (s, 1H), 7.76 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.37 (t, 1H), 4.15 (t, 2H), 3.95 (s, 3H), 3.47 (m, 2H), 2.43 (m, 2H), 2.41 (m, 8H), 2.36 (m, 2H), 1.94 (m, 2H).
MS (+ve ESI): 597.2 (M+H)$^+$

Example 66 - Preparation of compound 66 in table 3 - 2-{4-[(7-{3-[(cyclopropylmethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 47 but starting with (cyclopropylmethyl)amine (46 mg, 0.65 mmol) yielded compound 66 in table 3 (66 mg, 68 % yield):
^{1}H-NMR (DMSO d$_6$): 10.31 (s, 1H), 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.16 (s, 1H), 5.16 (s, 2H), 4.19 (t, 2H), 3.96 (s, 3H), 2.71 (t, 2H), 2.39 (d, 2H), 1.92 (m, 2H), 0.88 (m, 1H), 0.39 (m, 2H), 0.09 (m, 2H).
MS (+ve ESI): 538.1 (M+H)$^+$

Example 67 - Preparation of compound 67 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with 2-piperidin-4-ylethanol (84 mg, 0.65 mmol) yielded compound 67 in table 3 (102 mg, 95 % yield):

^{1}H-NMR (DMSO d_6): 9.41 (s, 1H), 8.20 (s, 1H), 8.07 (s, 1H), 7.51 (s, 1H), 7.49 (s, 1H), 7.45 (m, 1H), 6.91 (m, 2H), 6.86 (s, 1H), 4.88 (s, 2H), 4.03 (t, 1H), 3.87 (t, 2H), 3.67 (s, 3H), 3.14 (m, 2H), 2.57 (m, 2H), 2.14 (t, 2H), 1.65 (m, 2H), 1.56 (t, 2H), 1.33 (d, 2H), 1.06 (m, 3H), 0.86 (m, 2H).

MS (+ve ESI): 596.2 $(M+H)^+$

Example 68 - Preparation of compound 68 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(prop-2-yn-1-yl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with N-methylprop-2-yn-1-amine (45 mg, 0.65 mmol) yielded compound 68 in table 3 (55 mg, 57 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.15 (t, 2H), 3.96 (s, 3H), 3.13 (m, 1H), 2.51 (m, 4H), 2.23 (s, 3H), 1.93 (m, 2H).

MS (+ve ESI): 536.1 $(M+H)^+$

Example 69 - Preparation of compound 69 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[isobutyl(methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with N,2-dimethylpropan-1-amine (57 mg, 0.65 mmol) yielded compound 69 in table 3 (29 mg, 29 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.13 (s, 1H), 5.16 (s, 2H), 4.15 (t, 2H), 3.95 (s, 3H), 2.45 (m, 2H), 2.15 (s, 3H), 2.04 (d, 2H), 1.92 (m, 2H), 1.71 (m, 1H), 0.82 (d, 6H).

MS (+ve ESI): 554.2 $(M+H)^+$

Example 70 - Preparation of compound 70 in table 3 - *N*-(2,3-difluorophenyl)-2-[4-({7-[3-(3-hydroxypiperidin-1-yl)propoxy]-6-methoxyquinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 47 but starting with piperidin-3-ol (66 mg, 0.65 mmol) yielded compound 70 in table 3 (102 mg, 100 % yield):

^{1}H-NMR (DMSO d$_6$): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.61 (d, 1H), 4.16 (t, 2H), 3.96 (s, 3H), 3.47 (m, 1H), 2.83 (m, 1H), 2.66 (m, 1H), 2.44 (m, 2H), 1.93 (m, 2H), 1.85 (m, 1H), 1.75 (m, 2H), 1.61 (m, 1H), 1.41 (m, 1H), 1.07 (m, 1H).

MS (+ve ESI): 568.2 (M+H)$^+$

Example 71 - Preparation of compound 71 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with piperidin-4-ylmethanol (75 mg, 0.65 mmol) yielded compound 71 in table 3 (85 mg, 81 % yield):

^{1}H-NMR (DMSO d$_6$): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.41 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.24 (t, 2H), 2.87 (m, 2H), 2.43 (t, 2H), 1.95 (m, 2H), 1.85 (t, 2H), 1.63 (d, 2H), 1.33 (m, 1H), 1.13 (m, 2H).

MS (+ve ESI): 582.2 (M+H)$^+$

Example 72 - Preparation of compound 72 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(6-methoxy-7-{3-[methyl(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting methyl(propyl)amine (48 mg, 0.65 mmol) yielded compound 72 in table 3 (71 mg, 74 % yield):

^{1}H-NMR (DMSO d$_6$): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 2.46 (t, 2H), 2.26 (t, 2H), 2.16 (s, 3H), 1.92 (m, 2H), 1.41 (m, 2H), 0.83 (t, 3H).

MS (+ve ESI): 540.2 (M+H)$^+$

Example 73 - Preparation of compound 73 in table 3 - 2-{4-[(7-{3-[(cyclopropylmethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 47 but starting with (cyclopropylmethyl)propylamine (74 mg, 0.65 mmol) yielded compound 73 in table 3 (85 mg, 82 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.13 (s, 1H), 5.16 (s, 2H), 4.18 (t, 2H), 3.95 (s, 3H), 2.64 (m, 2H), 2.43 (t, 2H), 2.29 (d, 2H), 1.90 (m, 2H), 1.41 (m, 2H), 0.83 (t, 3H), 0.81 (m, 1H), 0.41 (m, 2H), 0.06 (m, 2H).

MS (+ve ESI): 580.2 $(M+H)^+$

Example 74 - Preparation of compound 74 in table 3 - 2-{4-[(7-{3-[[2-(diethylamino)ethyl](methyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 47 but starting with N,N-diethyl-N'-methylethane-1,2-diamine (85 mg, 0.65 mmol) yielded compound 74 in table 3 (55 mg, 51 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.95 (s, 3H), 2.41 (m, 10H), 2.19 (s, 3H), 1.91 (m, 2H), 0.90 (t, 6H).

MS (+ve ESI): 597.3 $(M+H)^+$

Example 75 - Preparation of compound 75 in table 3 - 2-{4-[(7-{3-[[2-(diethylamino)ethyl](ethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 47 but starting with N,N,N'-triethylethane-1,2-diamine (94 mg, 0.65 mmol) yielded compound 75 in table 3 (9 mg, 8 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.77 (s, 1H), 7.76 (s, 1H), 7.72 (m, 1H), 7.20 (m, 2H), 7.14 (s, 1H), 5.15 (s, 2H), 4.17 (t, 2H), 3.95 (s, 3H), 2.57 (t, 2H), 2.43 (m, 10H), 1.89 (m, 2H), 0.95 (t, 3H), 0.91 (t, 6H).

MS (+ve ESI): 611.2 $(M+H)^+$

Example 76 - Preparation of compound 76 in table 3 - *N*-(2,3-difluorophenyl)-2-[4-({6-methoxy-7-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]quinazolin-4-yl}amino)-1*H*-pyrazol-1-yl]acetamide

An analogous reaction to that described in example 47 but starting with 1-methyl-1,4-diazepane (74 mg, 0.65 mmol) yielded compound 76 in table 3 (52 mg, 50 % yield):

^{1}H-NMR (DMSO d_6): 9.69 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.95 (s, 3H), 2.63 (m, 10H), 2.23 (s, 3H), 1.91 (m, 2H), 1.71 (m, 2H).

MS (+ve ESI): 581.2 $(M+H)^+$

Example 77 - Preparation of compound 77 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isopropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with 2-(isopropylamino)ethanol (67 mg, 0.65 mmol) yielded compound 77 in table 3 (59 mg, 58 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.27 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.36 (m, 2H), 2.87 (m, 1H), 2.26 (t, 2H), 2.44 (t, 2H), 1.86 (m, 2H), 0.92 (d, 6H).

MS (+ve ESI): 570.3 $(M+H)^+$

Example 78 - Preparation of compound 78 in table 3 - 2-{4-[(7-{3-[cyclopropyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 47 but starting with 2-(cyclopropylamino)ethanol (66 mg, 0.65 mmol) yielded compound 78 in table 3 (58 mg, 56 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.31 (m, 1H), 4.13 (t, 2H), 3.96 (s, 3H), 3.51 (m, 2H), 2.77 (m, 2H), 2.64 (m, 2H), 1.97 (m, 2H), 1.83 (m, 1H), 0.43 (m, 2H), 0.31 (m, 2H).

MS (+ve ESI): 568.2 $(M+H)^+$

Example 79 - Preparation of compound 79 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with 2-((2-methoxyethyl)amino)ethanol (77 mg, 0.65 mmol) yielded compound 79 in table 3 (75 mg, 71 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.31 (t, 1H), 4.17 (t, 2H), 3.96 (s, 3H), 3.43 (m, 2H), 3.37 (m, 2H), 3.21 (s, 3H), 2.64 (m, 4H), 2.53 (m, 2H), 1.89 (m, 2H).

MS (+ve ESI): 586.2 $(M+H)^+$

Example 80 - Preparation of compound 80 in table 3 - 2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 47 but starting with 2-(cyclobutylamino)ethanol (75 mg, 0.65 mmol) yielded compound 80 in table 3 (49 mg, 47 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.49 (s, 1H), 8.48 (s, 1H), 7.81 (s, 1H), 7.78 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.35 (m, 1H), 4.15 (t, 2H), 3.95 (s, 3H), 3.40 (m, 2H), 3.12 (m, 1H), 2.56 (m, 2H), 2.46 (m, 2H), 1.95 (m, 2H), 1.89 (m, 2H), 1.76 (m, 2H), 1.54 (m, 2H).

MS (+ve ESI): 582.2 $(M+H)^+$

Example 81 - Preparation of compound 81 in table 3 - 2-{4-[(7-{3-[(cyclopropylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 47 but starting with 2-((cyclopropylmethyl)amino)ethanol (75 mg, 0.65 mmol) yielded compound 81 in table 3 (66 mg, 63 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.05 (s, 1H), 8.41 (s, 1H), 8.09 (s, 1H), 7.97 (s, 1H), 7.75 (m, 1H), 7.34 (s, 1H), 7.21 (m, 2H), 5.27 (s, 2H), 4.32 (m, 2H), 4.03 (s, 3H), 3.82 (m, 2H), 3.45 (m, 2H), 3.40 (m, 1H), 3.34 (m, 1H), 3.18 (m, 2H), 2.31 (m, 2H), 1.17 (m, 1H), 0.69 (m, 2H), 0.45 (m, 2H).

MS (+ve ESI): 582.2 (M+H)$^+$

Example 82 - Preparation of compound 82 in table 3 - 2-{4-[(7-{3-[(cyclobutylmethyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 47 but starting with 2-((cyclobutylmethyl)amino)ethanol (84 mg, 0.65 mmol) yielded compound 82 in table 3 (70 mg, 66 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.28 (m, 1H), 4.16 (t, 2H), 3.96 (s, 3H), 3.43 (m, 2H), 2.57 (m, 2H), 2.45 (m, 4H), 1.91 (m, 5H), 1.76 (m, 2H), 1.59 (m, 2H).

MS (+ve ESI): 596.2 (M+H)$^+$

Example 83 - Preparation of compound 83 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(prop-2-yn-1-yl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with 2-(prop-2-yn-1-ylamino)ethanol (64 mg, 0.65 mmol) yielded compound 83 in table 3 (68 mg, 67 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.22 (m, 2H), 7.16 (s, 1H), 5.16 (s, 2H), 4.43 (t, 1H), 4.15 (t, 2H), 3.96 (s, 3H), 3.44 (m, 2H), 3.38 (m, 2H), 3.09 (m, 1H), 2.63 (t, 2H), 2.54 (m, 2H), 1.92 (m, 2H).

MS (+ve ESI): 566.2 (M+H)$^+$

Example 84 - Preparation of compound 84 in table 3 - 2-{4-[(7-{3-[allyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

An analogous reaction to that described in example 47 but starting with 2-(allylamino)ethanol (66 mg, 0.65 mmol) yielded compound 84 in table 3 (73 mg, 71 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.72 (m, 1H), 7.22 (m, 2H), 7.15 (s, 1H), 5.82 (m, 1H), 5.17 (m, 1H), 5.16 (s, 2H), 5.09 (m, 1H), 4.35 (t, 1H), 4.16 (t, 2H), 3.95 (s, 3H), 3.44 (m, 2H), 3.32 (m, 2H), 3.1 (d, 2H), 2.62 (t, 2H), 1.91 (m, 2H).

MS (+ve ESI): 568.2 (M+H)$^+$

Example 85 - Preparation of compound 85 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2,2-dimethylpropyl)(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with 2-((2,2-dimethylpropyl)amino)ethanol (85 mg, 0.65 mmol) yielded compound 85 in table 3 (67 mg, 62 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.77 (s, 1H), 7.76 (s, 1H), 7.74 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.17 (s, 2H), 4.33 (t, 1H), 4.17 (t, 2H), 3.95 (s, 3H), 3.44 (m, 2H), 2.65 (m, 2H), 2.54 (m, 2H), 2.21 (s, 2H), 1.91 (m, 2H), 0.83 (s, 9H).

MS (+ve ESI): 598.2 $(M+H)^+$

Example 86 - Preparation of compound 86 in table 3 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(3,3,3-trifluoropropyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 47 but starting with 2-((3,3,3-trifluoropropyl)amino)ethanol (102 mg, 0.65 mmol) yielded compound 86 in table 3 (80 mg, 72 % yield):

^{1}H-NMR (DMSO d_6): 9.73 (s, 1H), 8.49 (s, 1H), 8.35 (s, 1H), 7.79 (s, 1H), 7.77 (s, 1H), 7.73 (m, 1H), 7.23 (m, 2H), 7.16 (s, 1H), 5.17 (s, 2H), 4.18 (t, 2H), 3.96 (s, 3H), 3.49 (m, 2H), 2.67 (m, 6H), 1.94 (m, 2H).

MS (+ve ESI): 624.2 $(M+H)^+$

Example 87 - Preparation of compound 87 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

2-(Propylamino)ethanol (95 mg, 0.92 mmol) was added to a solution of 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(2,3-difluorophenyl)acetamide (103 mg, 0.23 mmol) and potassium iodide (76 mg, 0.46 mmol) in dimethylacetamide (0.5 ml) and the mixture heated at 90 °C for 2 hours under argon. The reaction mixture was cooled and water (1 ml) was added resulting in precipitation. The solid was recovered by filtration, dissolved in dichloromethane: methanol (1:1) and the solution filtered through a teflon filter.

The solvent was evaporated and the residual oil triturated in dichloromethane: diethyl ether (1:1) to yield compound 87 in table 4 (70 mg, 56 % yield):
^{1}H-NMR (DMSO d_6, TFA): 9.01 (s, 1H), 8.62 (d, 1H), 8.41 (s, 1H), 7.98 (s, 1H), 7.72 (m, 1H), 7.51 (d, 1H), 7.27 (s, 1H), 7.20 (m, 2H), 5.25 (s, 2H), 4.30 (m, 2H), 3.78 (m, 2H), 3.34 (m, 2H), 3.27 (m, 2H), 3.15 (m, 2H), 2.25 (m, 2H), 1.71 (m, 2H), 0.94 (t, 3H).
MS (+ve ESI): 540.1 $(M+H)^+$

Example 88 - Preparation of compound 88 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(isobutyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 87 but starting with 2-(isobutylamino)ethanol (107 mg, 0.92 mmol) yielded compound 88 in table 4 (85 mg, 67 % yield):
^{1}H-NMR (DMSO d_6, TFA): 9.01 (s, 1H), 8.63 (d, 1H), 8.41 (s, 1H), 7.98 (s, 1H), 7.73 (m, 1H), 7.51 (d, 1H), 7.28 (s, 1H), 7.20 (m, 2H), 5.25 (s, 2H), 4.31 (m, 2H), 3.82 (m, 2H), 3.38 (m, 2H), 3.29 (m, 2H), 3.10 (m, 1H), 3.04 (m, 1H), 2.27 (m, 2H), 2.16 (m, 1H), 1.01 (d, 6H).
MS (+ve ESI): 554.2 $(M+H)^+$

Example 89 - Preparation of compound 89 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 87, but starting with (2S)-pyrrolidin-2-ylmethanol (93 mg, 0.92 mmol) yielded compound 89 in table 4 (83 mg, 67 % yield):
^{1}H-NMR (DMSO d_6, TFA): 9.01 (s, 1H), 8.63 (d, 1H), 8.41 (s, 1H), 7.98 (s, 1H), 7.73 (m, 1H), 7.50 (d, 1H), 7.27 (s, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.31 (t, 2H), 3.78 (m, 1H), 3.62 (m, 4H), 3.26 (m, 1H), 3.18 (m, 1H), 2.26 (m, 2H), 2.13 (m, 1H), 2.03 (m, 1H), 1.89 (m, 1H), 1.79 (m, 1H).
MS (+ve ESI): 538.2 $(M+H)^+$

Example 90 - Preparation of compound 90 in table 4 - *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 87, but starting with (2R)-pyrrolidin-2-ylmethanol (73 mg, 0.72 mmol) yielded compound 90 in table 4 (58 mg, 59 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.99 (s, 1H), 8.61 (d, 1H), 8.40 (s, 1H), 7.96 (s, 1H), 7.72 (m, 1H), 7.51 (d, 1H), 7.26 (s, 1H), 7.17 (m, 2H), 5.23 (s, 2H), 4.29 (t, 2H), 3.76 (m, 1H), 3.61 (m, 4H), 3.26 (m, 1H), 3.15 (m, 1H), 2.24 (m, 2H), 2.12 (m, 1H), 2.02 (m, 1H), 1.89 (m, 1H), 1.77 (m, 1H).

MS (+ve ESI): 538.2 $(M+H)^+$

Example 91 - Preparation of compound 91 in table 4- 2-{4-[(7-{3-[cyclopentyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide

The reaction was carried out in an analogous manner to that described in example 87, but starting with 2-(cyclopentylamino)ethanol (136 mg, 1.06 mmol). On completion of reaction, the reaction mixture was diluted with dichloromethane (10 ml) and loaded directly onto a silica gel chromatography column. Elution with dichloromethane followed by increased polarity to dichloromethane : methanol (20:1) then dichloromethane: methanol : ammonia (20:1:0.1) yielded compound 91 in table 4 (75 mg, 63 % yield):

^{1}H-NMR (DMSO d_6): 10.27 (br s, 1H), 9.91 (br s, 1H), 8.54 (s, 1H), 8.34 (m, 2H), 7.79 (s, 1H), 7.72 (m, 1H), 7.20 (m, 3H), 7.13 (s, 1H), 5.16 (s, 2H), 4.29 (s, 1H), 4.17 (t, 2H), 3.43 (m, 2H), 3.06 (m, 1H), 2.67 (t, 2H), 2.56 (s, 2H), 1.88 (m, 2H), 1.71 (m, 2H), 1.56 (m, 2H), 1.45 (m, 2H), 1.31 (m, 2H).

MS (+ve ESI): 566 $(M+H)^+$

Example 92 - Preparation of compound 92 in table 4- *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 91, but starting with 2-(ethylamino)ethanol (178 mg, 2 mmol) yielded compound 92 in table 4 (141 mg, 67 % yield):

^{1}H-NMR (DMSO d_6): 8.66 (s, 1H), 8.46 (m, 2H), 7.91 (s, 1H), 7.83 (m, 1H), 7.30 (m, 3H), 7.25 (m, 1H), 5.26 (s, 2H), 4.24 (s, 1H), 4.28 (t, 2H), 3.55 (m, 2H), 2.71 (t, 2H), 2.52 (m, 4H), 1.99 (m, 2H), 1.07 (t, 3H).

MS (+ve ESI): 526 (M+H)$^+$

Example 93 - Preparation of compound 93 in table 4- *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 91, but starting with 2-piperazin-1-ylethanol (138 mg, 1.06 mmol) yielded compound 93 in table 4 (78 mg, 65 % yield):

^{1}H-NMR (DMSO d_6): 10.26 (br s, 1H), 9.90 (br s, 1H), 8.54 (s, 1H), 8.33 (m, 2H), 7.78 (s, 1H), 7.70 (m, 1H), 7.18 (m, 3H), 7.13 (s, 1H), 5.16 (s, 2H), 4.31 (m, 1H), 4.16 (t, 2H), 3.46 (m, 2H), 2.38 (m, 12H), 1.92 (m, 2H).

MS (+ve ESI): 567 (M+H)$^+$

Example 94 - Preparation of compound 94 in table 4- *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 91, but starting with piperidin-4-ylmethanol (230 mg, 2 mmol) yielded compound 94 in table 4 (111 mg, 50 % yield):

^{1}H-NMR (DMSO d_6): 9.95 (br s, 1H), 8.56 (s, 1H), 8.39 (m, 1H), 8.34 (s, 1H), 7.79 (s, 1H), 7.70 (t, 1H), 7.19 (m, 4H), 5.16 (s, 2H), 4.60 (m, 1H), 4.24 (t, 2H), 3.55 (m, 2H), 3.25 (m, 4H), 2.92 (m, 2H), 2.17 (m, 2H), 1.95 (m, 2H), 1.63 (m, 1H), 1.39 (m, 2H).

MS (+ve ESI): 552 (M+H)$^+$

Example 95 - Preparation of compound 95 in table 4- *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 91, but starting with 3-amino-3methylbutan-1-ol (206 mg, 2 mmol) yielded compound 95 in table 4 (89 mg, 41 % yield):

^{1}H-NMR (DMSO d_6): 8.65 (s, 1H), 8.45 (m, 2H), 7.90 (s, 1H), 7.82 (m, 1H), 7.30 (m, 4H), 5.25 (s, 2H), 4.33 (t, 2H), 3.67 (t, 2H), 2.97 (t, 2H), 2.09 (m, 2H), 1.76 (t, 2H), 1.26 (s, 6H).

MS (+ve ESI): 540 (M+H)$^+$

Example 96 - Preparation of compound 96 in table 5- *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 91, but starting with 2-(propylamino)ethanol (129 mg, 1.25 mmol) and 2-(4-{[7-(3-chloropropoxy)quinazolin-4-yl]amino}-1*H*-pyrazol-1-yl)-*N*-(3-fluorophenyl)acetamide (113 mg, 0.25 mmol) yielded compound 96 in table 5 (60 mg, 46 % yield):

^{1}H-NMR (DMSO d_6): 10.50 (s, 1H), 9.90 (s, 1H), 8.45 (s, 1H), 8.32 (m, 2H), 7.78 (s, 1H), 7.56 (m, 1H), 7.34 (m, 1H), 7.31 (m, 1H), 7.20 (m, 1H), 7.11 (s, 1H), 6.90 (m, 1H), 5.04 (s, 2H), 4.26 (t, 1H), 4.16 (t, 2H), 2.60 (t, 2H), 2.48 (m, 2H), 2.38 (m, 2H), 1.87 (m, 2H), 1.38 (m, 2H), 0.81 (t, 3H).

MS (+ve ESI): 522 $(M+H)^+$

Example 97 - Preparation of compound 97 in table 5- 2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide

An analogous reaction to that described in example 96, but starting with 2-(ethylamino)ethanol (111 mg, 1.25 mmol) yielded compound 97 in table 5 (40 mg, 32 % yield):

^{1}H-NMR (DMSO d_6): 10.58 (s, 1H), 9.96 (s, 1H), 8.56 (s, 1H), 8.36 (m, 2H), 7.79 (s, 1H), 7.60 (m, 1H), 7.33 (m, 2H), 7.23 (m, 1H), 7.14 (s, 1H), 6.91 (m, 1H), 5.08 (s, 2H), 4.36 (br s, 1H), 4.19 (m, 2H), 3.46 (m, 2H), 2.61 (m, 2H), 2.51 (m, 4H), 1.90 (m, 2H), 0.98 (t, 3H).

MS (+ve ESI): 508 $(M+H)^+$

Example 98 - Preparation of compound 98 in table 5- *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 96, but starting with (2R)-pyrrolidin-2-ylmethanol (126 mg, 1.25 mmol) yielded compound 98 in table 5 (101 mg, 78 % yield):

^{1}H-NMR (DMSO d_6): 9.92 (br s, 1H), 8.55 (s, 1H), 8.35 (m, 2H), 7.77 (s, 1H), 7.59 (m, 1H), 7.33 (m, 2H), 7.22 (m, 1H), 7.15 (s, 1H), 6.90 (m, 1H), 5.05 (s, 2H), 4.40 (br s, 1H), 4.20 (t,

2H), 3.40 (m, 1H), 3.30 (m, 1H), 2.50 (m, 2H), 2.28 (m, 1H), 1.96 (m, 2H), 1.82 (m, 1H), 1.67 (m, 2H), 1.58 (m, 1H).

MS (+ve ESI): 520 $(M+H)^+$

Example 99 - Preparation of compound 99 in table 5- *N*-(3-fluorophenyl)-2-{4-[(7-{3-[4-(hydroxymethyl)piperidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 96, but starting with piperidin-4-ylmethanol (144 mg, 1.25 mmol) yielded compound 99 in table 5 (122 mg, 92 % yield):

^{1}H-NMR (DMSO d_6): 10.50 (br s, 1H), 9.92 (br s, 1H), 8.57 (s, 1H), 8.34 (m, 2H), 7.79 (s, 1H), 7.57 (m, 1H), 7.30 (m, 2H), 7.21 (m, 1H), 7.17 (s, 1H), 6.90 (m, 1H), 5.06 (s, 2H), 4.54 (br s, 1H), 4.21 (t, 2H), 3.31 (m, 2H), 2.98 (m, 2H), 2.50 (m, 4H), 2.10 (m, 2H), 1.79 (m, 2H), 1.53 (m, 1H), 1.30 (m, 2H).

MS (+ve ESI): 534 $(M+H)^+$

Example 100 - Preparation of compound 100 in table 5- *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

An analogous reaction to that described in example 96, but starting with 3-amino-3methylbutan-1-ol (129 mg, 1.25 mmol) yielded compound 100 in table 5 (105 mg, 81 % yield):

^{1}H-NMR (DMSO d_6): 10.51 (s, 1H), 9.91 (s, 1H), 8.56 (s, 1H), 8.36 (m, 1H), 8.33 (s, 1H), 7.77 (s, 1H), 7.58 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.23 (m, 1H), 7.16 (s, 1H), 6.91 (m, 1H), 5.05 (s, 2H), 4.24 (t, 2H), 3.58 (t, 2H), 2.97 (t, 2H), 2.03 (m, 2H), 1.70 (t, 2H), 1.22 (s, 6H).

MS (+ve ESI): 522 $(M+H)^+$

Example 101 - Preparation of compound 101 in table 6 - 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate

A solution of 4.0 N hydrochloric acid in dioxane (1.42 ml, 5.7 mmol) was added to a solution of di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate

(720 mg, 0.95 mmol) in dichloromethane (7 ml) and dioxane (20 ml) and the mixture was stirred at ambient temperature for 23 hours. The precipitate was filtered, washed with dichloromethane and diethyl ether and dried *in vacuo* (50 °C, 0.1 mm Hg) to yield compound 101 in table 6 (720 mg, 99.5 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.43 (s, 1H), 8.22 (s, 1H), 8.02 (s, 1H), 7.75 (m, 1H), 7.37 (s, 1H), 7.21 (m, 2H), 5.26 (s, 2H), 4.28 (m, 4H), 4.04 (s, 3H), 3.51 (m, 2H), 3.39 (m, 2H), 3.21 (m, 2H), 2.31 (m, 2H), 1.74 (m, 2H), 0.96 (t, 3H).

MS (+ve ESI): 650.5 $(M+H)^+$

Di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate used as starting material, was obtained as follows:

a) Di-tert-butyl diethylphosphoramidite (486 mg, 1.95 mmol) was added slowly to a solution of *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(propyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (740 mg, 1.3 mmol) and tetrazole (228 mg, 3.25 mmol) in dimethylformamide (7.4 ml) under argon. The mixture was stirred at ambient temperature for 45 minutes. Hydrogen peroxide (9 N, 288 μl, 2.6 mmol) was added at 0 °C and the reaction stirred for 1.5 hours at ambient temperature. An additional quantity of hydrogen peroxide (72 μl, 0.65 mmol) was added to the solution to complete the oxidation. The mixture was cooled to 0 °C and a saturated solution of sodium metabisulfite (388 mg, 2 ml) was added slowly with vigorous stirring. The mixture was stirred at ambient temperature for 20 minutes, diluted with water and the pH adjusted to 7 with an aqueous solution of sodium bicarbonate. The mixture was extracted with ethyl acetate (3 x 10 ml), dried and concentrated. Purification by silica gel chromatography, eluting with dichloromethane : methanol (98:2) followed by dichloromethane : methanolic ammonia (3 N) (9:1) yielded di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate (720 mg, 67 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.97 (s, 1H), 8.41 (s, 1H), 8.08 (s, 1H), 7.96 (s, 1H), 7.74 (m, 1H), 7.35 (s, 1H), 7.20 (m, 2H), 5.25 (s, 2H), 4.27 (m, 4H), 4.02 (s, 3H), 3.52 (m, 2H), 3.37 (m, 2H), 3.21 (m, 2H), 2.29 (m, 2H), 1.72 (m, 2H), 1.44 (s, 18H), 0.95 (t, 3H), 1.44 (s, 18H).

MS (+ve ESI): 762.8 $(M+H)^+$

Example 102 - Preparation of compound 102 in table 6 - {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 101, but starting with di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (502 mg, 0.66 mmol) yielded compound 102 in table 6 (462 mg, 88 % yield):

^{1}H-NMR (DMSO d$_6$, TFA): 8.96 (s, 1H), 8.43 (s, 1H), 8.23 (m, 1H), 8.02 (s, 1H), 7.74 (m, 1H), 7.37 (s, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.31 (m, 2H), 4.20 (m, 2H), 4.04 (s, 3H), 3.83 (m, 1H), 3.71 (m, 1H), 3.61 (m, 1H), 3.24 (m, 2H), 2.32 (m, 2H), 2.22 (m, 1H), 2.05 (m, 1H), 1.95 (m, 1H), 1.86 (m, 1H).

MS (+ve ESI): 648.0 (M+H)$^+$

di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate used as starting material was obtained as follows:

An analogous reaction to that described in example 101a, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (1.08 g, 1.9 mmol) yielded di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (512 mg, 35 % yield):

^{1}H-NMR (DMSO d$_6$): 10.32 (s, 1H), 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.77 (m, 2H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.16 (m, 2H), 3.95 (s, 3H), 3.77 (m, 1H), 3.57 (m, 1H), 3.08 (m, 1H), 2.93 (m, 1H), 2.67 (m, 1H), 2.47 (m, 1H), 2.21 (m, 1H), 1.95 (m, 2H), 1.86 (m, 1H), 1.69 (m, 2H), 1.6 (m, 1H), 1.36 (s, 18H).

MS (+ve ESI): 760.4 (M+H)$^+$

Example 103 - Preparation of compound 103 in table 6 - {(2*S*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 101, but starting with di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-

methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (605 mg, 0.96 mmol) yielded compound 103 in table 6 (595 mg, 76 % yield):

^{1}H-NMR (DMSO d_6, CD_3COOD): 8.93 (s, 1H), 8.45 (s, 1H), 8.30 (m, 1H), 8.05 (s, 1H), 7.62 (m, 1H), 7.39 (s, 1H), 7.36 (m, 2H), 6.91 (m, 1H), 5.17 (s, 2H), 4.31 (m, 2H), 4.24 (m, 2H), 4.05 (s, 3H), 3.84 (m, 1H), 3.71 (m, 1H), 3.61 (m, 1H), 3.33 (m, 1H), 3.25 (m, 1H), 2.34 (m, 2H), 2.23 (m, 1H), 2.06 (m, 1H), 1.97 (m, 1H), 1.89 (m, 1H).

MS (+ve ESI): 530.2 $(M+H)^+$

di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate used as starting material was obtained as follows:

An analogous reaction to that described in example 101a, but starting with *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (1.12 g, 2.04 mmol) yielded di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (618 mg, 41 % yield):

^{1}H-NMR (DMSO d_6): 10.56 (s, 1H), 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (m, 1H), 7.36 (m, 1H), 7.32 (m, 1H), 7.15 (s, 1H), 6.92 (m, 1H), 5.06 (s, 2H), 4.16 (m, 2H), 3.96 (s, 3H), 3.78 (m, 1H), 3.56 (m, 1H), 3.08 (m, 1H), 2.93 (m, 1H), 2.67 (m, 1H), 2.49 (m, 1H), 2.21 (m, 1H), 1.95 (m, 2H), 1.86 (m, 1H), 1.69 (m, 2H), 1.62 (m, 1H), 1.37 (s, 18H).

MS (+ve ESI): 742.4 $(M+H)^+$

Example 104 - Preparation of compound 104 in table 6 - 2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 101, but starting with di-*tert*-butyl 2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (610 mg, 0.84 mmol) yielded compound 104 in table 6 (589 mg, 89 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.95 (s, 1H), 8.44 (s, 1H), 8.32 (m, 1H), 8.04 (s, 1H), 7.61 (m, 1H), 7.36 (m, 3H), 6.92 (m, 1H), 5.16 (s, 2H), 4.31 (m, 2H), 4.25 (m, 2H), 4.04 (s, 3H), 3.48 (m, 2H), 3.37 (m, 4H), 2.30 (m, 2H), 1.28 (t, 3H).

MS (+ve ESI): 618.1 $(M+H)^+$

di-*tert*-butyl 2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate used as starting material was obtained as follows:

An analogous reaction to that described in example 101a, but starting with 2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide (645 mg, 1.2 mmol) yielded di-*tert*-butyl 2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (620 mg, 71 % yield):

^{1}H-NMR (DMSO d_6): 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (d, 1H), 7.38 (q, 1H), 7.32 (d, 1H), 7.14 (s, 1H), 6.91 (t, 1H), 5.06 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 3.86 (m, 2H), 2.67 (t, 2H), 2.62 (t, 2H), 2.54 (m, 2H), 1.90 (m, 2H), 0.97 (t, 3H), 1.38 (s, 18H).

MS (+ve ESI): 730.2 $(M+H)^+$

Example 105 - Preparation of compound 105 in table 6 - {(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 101, but starting with di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (477 mg, 0.64 mmol) yielded compound 105 in table 6 (430 mg, 90 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.43 (s, 1H), 8.27 (m, 1H), 8.02 (s, 1H), 7.62 (m, 1H), 7.37 (m, 3H), 6.92 (m, 1H), 5.16 (s, 2H), 4.31 (m, 2H), 4.21 (m, 2H), 4.04 (s, 3H), 3.83 (m, 1H), 3.71 (m, 1H), 3.61 (m, 1H), 3.31 (m, 1H), 3.24 (m, 1H), 2.32 (m, 2H), 2.21 (m, 1H), 2.05 (m, 1H), 1.94 (m, 1H), 1.85 (m, 1H).

MS (+ve ESI): 630.2 $(M+H)^+$

di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate used as starting material was obtained as follows:

An analogous reaction to that described in example 101a, but starting with *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (588 mg, 1.07 mmol) yielded di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (367 mg, 46 % yield):

^{1}H-NMR (DMSO d_6): 10.56 (s, 1H), 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.59 (d, 1H), 7.37 (q, 1H), 7.32 (d, 1H), 7.15 (s, 1H), 6.91 (t, 1H), 5.06 (s, 1H), 4.17 (m, 2H), 3.96 (s, 3H), 3.56 (m, 1H), 3.08 (m, 1H), 2.94 (m, 1H), 2.67 (m, 1H), 2.21 (m, 1H), 1.95 (m, 2H), 1.86 (m, 1H), 1.69 (m, 2H), 1.62 (m, 1H), 1.37 (s, 18H).

MS (+ve ESI): 742.4 $(M+H)^+$

Example 106 - Preparation of compound 106 in table 6 - 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 101, but starting with di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl phosphate (540 mg, 0.69 mmol) yielded compound 106 in table 6 (462 mg, 90 % yield):

^{1}H-NMR (DMSO d_6, CD_3COOD): 8.87 (s, 1H), 8.44 (s, 1H), 8.31 (s, 1H), 8.07 (s, 1H), 7.74 (m, 1H), 7.48 (s, 1H), 7.18 (m, 2H), 5.25 (s, 2H), 4.34 (m, 2H), 4.25 (m, 2H), 3.77 (s, 3H), 3.76 (m, 2H), 3.52 (m, 2H), 3.46 (m, 2H), 3.42 (m, 2H), 3.34 (s, 3H), 2.30 (m, 2H).

MS (+ve ESI): 666.0 $(M+H)^+$

di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl phosphate used as starting material was obtained as follows:

An analogous reaction to that described in example 101a, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (640 mg, 1.09 mmol) yielded di-

tert-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl phosphate (550 mg, 65 % yield):

^{1}H-NMR (DMSO d_6): 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.15 (s, 2H), 4.16 (t, 2H), 3.96 (s, 3H), 3.85 (m, 2H), 3.38 (t, 2H), 2.73 (t, 2H), 2.68 (m, 4H), 1.90 (m, 2H), 1.38 (s, 18H).

MS (+ve ESI): 778.4 (M+H)$^+$

Example 107 - Preparation of compound 107 in table 6 - {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 101, but starting with di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (593 mg, 0.81 mmol) yielded compound 107 in table 6 (559 mg, 100 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.00 (s, 1H), 8.71 (d, 1H), 8.42 (s, 1H), 8.01 (s, 1H), 7.74 (m, 1H), 7.51 (dd, 1H), 7.31 (d, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.31 (m, 2H), 4.21 (m, 2H), 3.81 (m, 1H), 3.69 (m, 1H), 3.61 (m, 1H), 3.33 (m, 1H), 3.23 (m, 1H), 2.28 (m, 2H), 2.20 (m, 1H), 2.05 (m, 1H), 1.95 (m, 1H), 1.84 (m, 1H).

MS (+ve ESI): 618.2 (M+H)$^+$

di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate used as starting material was obtained as follows:

An analogous reaction to that described in example 101a, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (698 mg, 1.3 mmol) yielded di-*tert*-butyl {(2*S*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (665 mg, 70 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.02 (s, 1H), 8.64 (d, 1H), 8.41 (s, 1H), 7.98 (s, 1H), 7.74 (m, 1H), 7.51 (m, 1H), 7.27 (m, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.31 (m, 2H), 4.20 (m, 2H), 3.82 (m, 1H), 3.71 (m, 1H), 3.61 (m, 1H), 3.32 (m, 1H), 3.26 (m, 1H), 2.26 (m, 3H), 2.08 (m, 1H), 1.94 (m, 1H), 1.83 (m, 1H), 1.45 (s, 18H).

MS (+ve ESI): 730.6 $(M+H)^+$

Example 108 - Preparation of compound 108 in table 6 - {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 101, but starting with di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (651 mg, 0.89 mmol) yielded compound 108 in table 6 (608 mg, 97 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.01 (s, 1H), 8.72 (d, 1H), 8.43 (s, 1H), 8.02 (s, 1H), 7.74 (s, 1H), 7.51 (m, 1H), 7.32 (m, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.32 (m, 2H), 4.21 (m, 2H), 3.82 (m, 1H), 3.68 (m, 1H), 3.62 (m, 1H), 3.32 (m, 1H), 3.23 (m, 1H), 2.29 (m, 2H), 2.21 (m, 1H), 2.06 (m, 1H), 1.94 (m, 1H), 1.84 (m, 1H).

MS (+ve ESI): 618.3 $(M+H)^+$

di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate used as starting material was obtained as follows:

An analogous reaction to that described in example 101a, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (688 mg, 1.3 mmol) yielded di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (665 mg, 70 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.02 (s, 1H), 8.64 (d, 1H), 8.41 (s, 1H), 7.99 (s, 1H), 7.74 (m, 1H), 7.51 (m, 1H), 7.27 (m, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.31 (m, 2H), 4.20 (m, 2H), 3.83 (m, 1H), 3.71 (m, 1H), 3.61 (m, 1H), 3.32 (m, 1H), 3.26 (m, 1H), 2.26 (m, 3H), 2.09 (m, 1H), 1.94 (m, 1H), 1.83 (m, 1H), 1.45 (s, 18H).

MS (+ve ESI): 730.6 $(M+H)^+$

Example 109 - Preparation of compound 109 in table 6 - {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 101, but starting with di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(2;3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (840 mg, 1.1 mmol) yielded compound 109 in table 6 (742 mg, 90 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.42 (s, 1H), 8.22 (m, 1H), 8.01 (s, 1H), 7.74 (m, 1H), 7.37 (s, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.30 (m, 2H), 4.21 (m, 2H), 4.04 (s, 3H), 3.83 (m, 1H), 3.70 (m, 1H), 3.62 (m, 1H), 3.31 (m, 1H), 3.24 (m, 1H), 2.32 (m, 2H), 2.21 (m, 1H), 2.05 (m, 1H), 1.93 (m, 1H), 1.60 (m, 1H).

MS (+ve ESI): 648.3 (M+H)$^+$

di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate used as starting material was obtained as follows:

An analogous reaction to that described in example 101a, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (777 mg, 1.37 mmol) yielded di-*tert*-butyl {(2*R*)-1-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl phosphate (0.84 g, 76 % yield):

^{1}H-NMR (DMSO d_6): 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.77 (s, 1H), 7.76 (s, 1H), 7.31 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.16 (m, 2H), 3.95 (s, 3H), 3.76 (m, 1H), 3.55 (m, 1H), 3.08 (m, 1H), 2.94 (m, 1H), 2.67 (m, 1H), 2.50 (m, 1H), 2.21 (m, 1H), 1.95 (m, 2H), 1.86 (m, 1H), 1.69 (m, 2H), 1.62 (m, 1H), 1.36 (s, 18H).

MS (+ve ESI): 760.6 (M+H)$^+$

Example 110 - Preparation of compound 110 in table 6 - 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 101, but starting with di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-

methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl phosphate (773 mg, 0.97 mmol) yielded compound 110 in table 6 (693 mg, 98 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.42 (s, 1H), 8.23 (m, 1H), 8.01 (s, 1H), 7.74 (m, 1H), 7.36 (s, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.29 (m, 2H), 4.23 (m, 2H), 4.04 (s, 3H), 3.49 (m, 2H), 3.35 (m, 4H), 2.31 (m, 2H), 1.28 (t, 3H).

MS (+ve ESI): 636.3 $(M+H)^+$

di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl phosphate used as starting material was obtained as follows:

An analogous reaction to that described in example 101a, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (790 mg, 1.42 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl phosphate (780 mg, 78 % yield):

^{1}H-NMR (DMSO d_6): 9.67 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.14 (s, 1H), 5.16 (s, 2H), 4.16 (t, 2H), 3.95 (s, 3H), 3.85 (m, 2H), 2.66 (t, 2H), 2.62 (t, 2H), 2.53 (t, 2H), 1.91 (m, 2H), 1.38 (s, 18H), 0.97 (t, 3H), 1.50 (s, 18H).

MS (+ve ESI): 748.5 $(M+H)^+$

Example 111 - Preparation of compound 111 in table 6 - 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 101, but starting with di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate (510 mg, 0.7 mmol) yielded compound 111 in table 6 (460 mg, 95 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.98 (s, 1H), 8.67 (d, 1H), 8.39 (s, 1H), 7.98 (s, 1H), 7.71 (m, 1H), 7.49 (d, 1H), 7.28 (s, 1H), 7.17 (m, 2H), 5.22 (s, 2H), 4.29 (m, 2H), 4.22 (m, 2H), 3.47 (m, 2H), 3.36 (m, 2H), 3.14 (m, 2H), 2.25 (m, 2H), 1.71 (m, 2H), 0.92 (t, 3H).

MS (+ve ESI): 620.2 $(M+H)^+$

di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate used as starting material was obtained as follows:

An analogous reaction to that described in example 101a, but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(2 hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (377 mg, 0.7 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphate (310 mg, 61 % yield):

^{1}H-NMR (DMSO d_6, TFA): 9.02 (s, 1H), 8.63 (d, 1H), 8.41 (s, 1H), 7.99 (s, 1H), 7.74 (m, 1H), 7.51 (d, 1H), 7.27 (s, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.31 (m, 2H), 4.25 (m, 2H), 3.51 (m, 2H), 3.38 (m, 2H), 3.18 (m, 2H), 2.25 (m, 2H), 1.70 (m, 2H), 0.95 (t, 3H), 1.45 (s, 18H).

MS (+ve ESI): 732.5 $(M+H)^+$

Example 112 - Preparation of compound 112 in table 6 - 2-{cyclobutyl[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 101, but starting with di-*tert*-butyl 2-{cyclobutyl[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (500 mg, 0.65 mmol) yielded compound 112 in table 6 (450 mg, 95 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.92 (s, 1H), 8.42 (s, 1H), 8.31 (m, 1H), 8.03 (s, 1H), 7.72 (m, 1H), 7.35 (s, 1H), 7.19 (m, 1H), 5.23 (s, 2H), 4.27 (m, 2H), 4.21 (m, 2H), 4.02 (s, 3H), 3.92 (m, 1H), 3.37 (m, 2H), 3.25 (m, 2H), 2.34 (m, 2H), 2.24 (m, 4H), 1.74 (m, 1H), 1.65 (m, 1H).

MS (+ve ESI): 662.4 $(M+H)^+$

di-*tert*-butyl 2-{cyclobutyl[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate used as starting material was obtained as follows:

An analogous reaction to that described in example 101a, but starting with 2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(2,3-difluorophenyl)acetamide (740 mg, 1.27 mmol) yielded di-*tert*-butyl 2-{cyclobutyl[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (657 mg, 67 % yield):

^{1}H-NMR (DMSO d_6): 9.68 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.73 (m, 1H), 7.21 (m, 2H), 7.15 (s, 1H), 5.16 (s, 2H), 4.15 (t, 2H), 3.95 (s, 3H), 3.84 (m, 2H), 3.16 (m, 1H), 2.65 (t, 2H), 2.59 (t, 2H), 1.96 (m, 2H), 1.88 (m, 2H), 1.77 (m, 2H), 1.55 (m, 2H), 1.39 (s, 18H).

MS (+ve ESI): 774.6 $(M+H)^+$

Example 113 - Preparation of compound 113 in table 6 - 2-{cyclobutyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 101, but starting with di-*tert*-butyl 2-{cyclobutyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (530 mg, 0.7 mmol) yielded compound 113 in table 6 (540 mg, 100 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.93 (s, 1H), 8.42 (s, 1H), 8.21 (m, 1H), 7.98 (s, 1H), 7.58 (d, 1H), 7.34 (m, 3H), 6.89 (m, 1H), 5.13 (s, 2H), 4.27 (m, 2H), 4.19 (m, 2H), 4.01 (s, 3H), 3.93 (m, 1H), 3.36 (m, 2H), 3.25 (m, 2H), 2.35 (m, 2H), 2.25 (m, 4H), 1.75 (m, 1H), 1.68 (m, 1H).

MS (+ve ESI): 644.3 $(M+H)^+$

di-*tert*-butyl 2-{cyclobutyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate used as starting material was obtained as follows:

An analogous reaction to that described in example 101a, but starting with 2-{4-[(7-{3-[cyclobutyl(2-hydroxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide (524 mg, 0.93 mmol) yielded di-*tert*-butyl 2-{cyclobutyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl]amino}ethyl phosphate (535 mg, 76 % yield):

^{1}H-NMR (DMSO d_6): 10.55 (s, 1H), 9.67 (s,.1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.59 (d, 1H), 7.38 (q, 1H), 7.31 (d, 1H), 7.14 (s, 1H), 6.91 (m, 1H), 5.06 (s, 2H), 4.15 (t, 2H), 3.95 (s, 3H), 3.85 (m, 2H), 3.16 (m, 1H), 2.64 (t, 2H), 2.59 (t, 2H), 1.96 (m, 2H), 1.88 (m, 2H), 1.77 (m, 2H), 1.56 (m, 2H), 1.38 (s, 18H).

MS (+ve ESI): 756.1 $(M+H)^+$

Example 114 - Preparation of compound 114 in table 6 - 2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 101, but starting with (325 mg, 0.43 mmol) yielded compound 114 in table 6 (329 mg, 100 % yield):

^{1}H-NMR (DMSO d_6, TFA): 8.96 (s, 1H), 8.42 (s, 1H), 8.22 (m, 1H), 8.00 (s, 1H), 7.61 (m, 1H), 7.36 (m, 3H), 6.92 (m, 1H), 5.15 (s, 2H), 4.30 (m, 2H), 4.25 (m, 2H), 4.04 (s, 3H), 3.74 (m, 2H), 3.56 (m, 2H), 3.49 (m, 2H), 3.42 (m, 2H), 3.34 (s, 3H), 2.37 (m, 2H).

MS (+ve ESI): 648.7(M+H)$^+$

di-*tert*-butyl 2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl phosphate used as starting material was obtained as follows:

An analogous reaction to that described in example 101a, but starting with *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2-hydroxyethyl)(2-methoxyethyl)amino]propoxy}-6-methoxyquinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (444 mg, 0.78 mmol) yielded di-*tert*-butyl 2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]-6-methoxyquinazolin-7-yl}oxy)propyl](2-methoxyethyl)amino]ethyl phosphate (325 mg, 55 % yield):

^{1}H-NMR (DMSO d_6): 10.55 (s, 1H), 9.67 (s, 1H), 8.47 (s, 1H), 8.34 (s, 1H), 7.77 (s, 1H), 7.75 (s, 1H), 7.58 (d, 1H), 7.37 (q, 1H), 7.31 (d, 1H), 7.14 (s, 1H), 6.91 (m, 1H), 5.06 (s, 2H), 4.16 (m, 2H), 3.95 (s, 3H), 3.85 (m, 2H), 3.38 (m, 2H), 3.2 (s, 3H), 2.73 (m, 2H), 2.67 (m, 4H), 1.91 (m, 2H), 1.37 (s, 18H).

MS (+ve ESI): 760.6 (M+H)$^+$

Example 115 - Preparation of compound 115 in table 6- 2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl dihydrogen phosphate

Di-*tert*-butyl diethylphosphoramidite (747 mg, 3 mmol) was added slowly to a solution of *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2 hydroxyethyl)(propyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (390 mg, 0.75 mmol) and tetrazole (158 mg, 2.25 mmol) in dimethylacetamide (4 ml) under nitrogen. The mixture was stirred at ambient temperature for 1 hour. Hydrogen peroxide (383 µl, 3.38 mmol, 30 % aqueous solution) was added slowly at 0 °C and the reaction mixture stirred for 1.5 hours at ambient temperature. An

additional portion of hydrogen peroxide (42 μl, 0.37 mmol) was added to the solution to complete the oxidation. The mixture was cooled to 0 °C and a saturated solution of sodium metabisulfite (7 ml of 0.53 M solution) added slowly with vigorous stirring. The mixture was stirred at ambient temperature for 20 minutes, diluted with water and the pH adjusted to 7 with an aqueous solution of potassium hydrogen carbonate. The reaction mixture was extracted with dichloromethane (3 x 25 ml) and the combined organics dried and concentrated *in vacuo*. Purification by silica gel chromatography, eluting with dichloromethane followed by increased polarity to dichloromethane : methanol : ammonia (20:1:0.1 to 20: 3: 0.2) gave di-*tert*-butyl 2-[[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](propyl)amino]ethyl phosphite as a pale yellow oil. This intermediate was dissolved in dioxane (10 ml) and a solution of 4.0 N hydrochloric acid in dioxane (1.12 ml, 4.5 mmol) added. The mixture was stirred at ambient temperature for 18 hours. The solid was filtered, washed with dichloromethane and diethyl ether and dried *in vacuo* for 18 hours (50 °C, 0.1 mm Hg) to yield compound 115 in table 6 as the dihydrochloride salt (375 mg, 70 % yield):

^{1}H-NMR (DMSO d_6, CD_3CO_2D): 8.93 (s, 1H), 8.80 (m, 1H), 8.41 (s, 1H), 8.01 (s, 1H), 7.58 (m, 1H), 7.45 (m, 1H), 7.32 (m, 3H), 6.88 (m, 1H), 5.12 (s, 2H), 4.29 (m, 4H), 3.46 (m, 2H), 3.35 (m, 2H), 3.14 (m, 2H), 2.28 (m, 2H), 1.73 (m, 2H), 0.93 (t, 3H).

MS (+ve ESI): 602 $(M+H)^+$

Example 116 - Preparation of compound 116 in table 6- 2-{4-[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]piperazin-1-yl}ethyl dihydrogen phosphate

An analogous reaction to that described in example 115 but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[4-(2-hydroxyethyl)piperazin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (363 mg, 0.64 mmol) yielded compound 116 in table 6 (442 mg, 91 % yield):

^{1}H-NMR (DMSO d_6, CD_3CO_2D): 8.94 (s, 1H), 8.84 (m, 1H), 8.42 (s, 1H), 8.04 (s, 1H), 7.70 (m, 1H), 7.47 (m, 1H), 7.36 (m, 1H), 7.17 (m, 2H), 5.22 (s, 2H), 4.33 (m, 2H), 4.27 (m, 2H), 3.72 (m, 8H), 3.51 (m, 2H), 3.41 (m, 2H), 2.33 (m, 2H).

MS (+ve ESI): 647 $(M+H)^+$

Example 117 - Preparation of compound 117 in table 6- 2-{ethyl[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}ethyl dihydrogen phosphate

An analogous reaction to that described in example 115 but starting with 2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}-*N*-(3-fluorophenyl)acetamide (362 mg, 0.71 mmol) yielded compound 117 in table 6 (246 mg, 50 % yield):

^{1}H-NMR (DMSO d_6, CD_3CO_2D): 8.92 (s, 1H), 8.80 (m, 1H), 8.40 (s, 1H), 8.01 (s, 1H), 7.58 (m, 1H), 7.47 (m, 1H), 7.33 (m, 3H), 6.88 (m, 1H), 5.13 (s, 2H), 4.28 (m, 4H), 3.45 (m, 2H), 3.36 (m, 2H), 3.28 (m, 2H), 2.28 (m, 2H), 1.28 (t, 3H).

MS (+ve ESI): 588 $(M+H)^+$

Example 118 - Preparation of compound 118 in table 6- 2-[[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl](ethyl)amino]ethyl dihydrogen phosphate

An analogous reaction to that described in example 115 but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[ethyl(2-hydroxyethyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide (368 mg, 0.70 mmol) yielded compound 118 in table 6 (313 mg, 63 % yield):

^{1}H-NMR (DMSO d_6, CD_3CO_2D): 8.91 (s, 1H), 8.77 (m, 1H), 8.40 (s, 1H), 8.01 (s, 1H), 7.68 (m, 1H), 7.45 (m, 1H), 7.34 (s, 1H), 7.16 (m, 2H), 5.20 (s, 2H), 4.28 (m, 2H), 4.25 (m, 2H), 3.43 (m, 2H), 3.34 (m, 2H), 3.25 (m, 2H), 2.25 (m, 2H), 1.27 (t, 3H).

MS (+ve ESI): 606 $(M+H)^+$

Example 119 - Preparation of compound 119 in table 6- 3-{[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}-3-methylbutyl dihydrogen phosphate

An analogous reaction to that described in example 115 but starting with *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1-dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

(379 mg, 0.72 mmol) yielded compound 119 in table 6 (365 mg, 71 % yield):

^{1}H-NMR (DMSO d_6, CD_3CO_2D): 8.91 (s, 1H), 8.74 (d, 1H), 8.39 (s, 1H), 8.00 (s, 1H), 7.55 (m, 1H), 7.47 (m, 1H), 7.31 (m, 3H), 6.85 (m, 1H), 5.10 (s, 2H), 4.31 (m, 2H), 4.00 (m, 2H), 3.10 (m, 2H), 2.23 (m, 2H), 2.02 (m, 2H), 1.34 (s, 6H).

MS (+ve ESI): 602 $(M+H)^+$

Example 120 - Preparation of compound 120 in table 6- 3-{[3-({4-[(1-{2-[(2,3-difluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]amino}-3-methylbutyl dihydrogen phosphate

An analogous reaction to that described in example 115 but starting with *N*-(2,3-difluorophenyl)-2-{4-[(7-{3-[(3-hydroxy-1,1 dimethylpropyl)amino]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

(353 mg, 0.65 mmol) yielded compound 120 in table 6 (310 mg, 65 % yield):

^{1}H-NMR (DMSO d_6, CD_3CO_2D): 9.14 (m, 1H), 8.95 (m, 1H), 8.42 (s, 1H), 8.04 (s, 1H), 7.71 (m, 1H), 7.50 (m, 1H), 7.37 (m, 1H), 7.19 (m, 2H), 5.23 (m, 2H), 4.34 (m, 2H), 4.00 (m, 2H), 3.11 (m, 2H), 2.26 (m, 2H), 2.04 (m, 2H), 1.36 (s, 6H).

MS (+ve ESI): 620 $(M+H)^+$

Example 121 - Preparation of compound 121 in table 6- {(2*R*)-1-[3-({4-[(1-{2-[(3-fluorophenyl)amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)amino]quinazolin-7-yl}oxy)propyl]pyrrolidin-2-yl}methyl dihydrogen phosphate

An analogous reaction to that described in example 115 but starting with *N*-(3-fluorophenyl)-2-{4-[(7-{3-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy}quinazolin-4-yl)amino]-1*H*-pyrazol-1-yl}acetamide

(397 mg, 0.76 mmol) yielded compound 121 in table 6 (429 mg, 79 % yield):

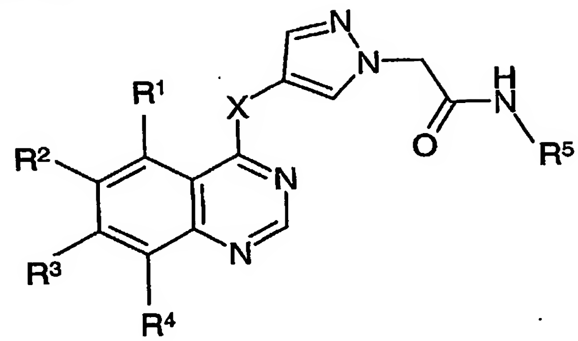
^{1}H-NMR (DMSO d_6, CD_3CO_2D): 8.92 (m, 1H), 8.76 (m, 1H), 8.40 (s, 1H), 8.00 (s, 1H), 7.56 (m, 1H), 7.46 (m, 1H), 7.31 (m, 2H), 6.85 (m, 1H), 5.10 (s, 2H), 4.29 (m, 2H), 4.20 (m, 2H), 3.78 (m, 1H), 3.64 (m, 1H), 3.59 (m, 1H), 3.29 (m, 1H), 3.18 (m, 1H), 2.27 (m, 2H), 2.18 (m, 1H), 2.01 (m, 1H), 1.94 (m, 1H), 1.80 (m, 1H).

MS (+ve ESI): 600 $(M+H)^+$

CLAIMS

What we claim is:

1. A compound of formula (I)



formula (I)

or a salt, ester or prodrug thereof;

where:

X is O or NR^6;

$\mathbf{R^6}$ is hydrogen or $C_{1\text{-}4}$alkyl;

$\mathbf{R^1}$ is hydrogen, halo, or $-X^1R^{11}$;

$\mathbf{X^1}$ is a direct bond, -O-, -NH- or $-N(C_{1\text{-}6}alkyl)$-;

$\mathbf{R^{11}}$ is hydrogen, heterocyclyl or a group selected from $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}6}$cycloalkyl and $C_{3\text{-}6}$cycloalkenyl where the group is optionally substituted by heterocyclyl, halo, hydroxy $C_{1\text{-}4}$alkoxy or $-NR^9R^{10}$;

$\mathbf{R^2}$ is hydrogen, halo, nitro, cyano or $-X^2R^{12}$;

$\mathbf{X^2}$ is a direct bond, -O-, -NH- or $-N(C_{1\text{-}6}alkyl)$-;

$\mathbf{R^{12}}$ is hydrogen, heterocyclyl or a group selected from aryl, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}6}$cycloalkyl and $C_{3\text{-}6}$cycloalkenyl where the group is optionally substituted by aryl, heterocyclyl, halo, hydroxy or $-NR^{15}R^{16}$;

$\mathbf{R^3}$ is hydrogen, halo or $-X^3R^{13}$;

$\mathbf{X^3}$ is a direct bond, $-CH_2{=}CH_2-$, -O-, -NH- or $-N(C_{1\text{-}6}alkyl)$-;

$\mathbf{R^{13}}$ is hydrogen, heterocyclyl or a group selected from $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}6}$cycloalkyl and $C_{3\text{-}6}$cycloalkenyl where the group is optionally substituted by $-NR^7R^8$, heterocyclyl, halo, hydroxy or $C_{1\text{-}4}$alkoxy;

R^7 and **R^8** are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, hydroxyC_{3-6}cycloalkyl, hydroxyC_{1-4}alkylC_{3-6}cycloalkyl, hydroxyC_{3-6}cycloalkylC_{1-3}alkyl, C_{1-3}alkoxyC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{3-6}cycloalkylC_{1-3}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-3}alkylaminoC_{1-6}alkyl and di(C_{1-3}alkyl)aminoC_{1-6}alkyl;

or **R^7** and **R^8** together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is optionally substituted on carbon or nitrogen by 1 or 2 groups independently selected from C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkoxyC_{1-4}alkoxy, and where a ring $-CH_2-$ is optionally replaced with $-C(O)-$;

R^4 is selected from hydrogen, halo or $-X^4R^{14}$;

X^4 is a direct bond, -O-, -NH- or $-N(C_{1-6}$alkyl)-;

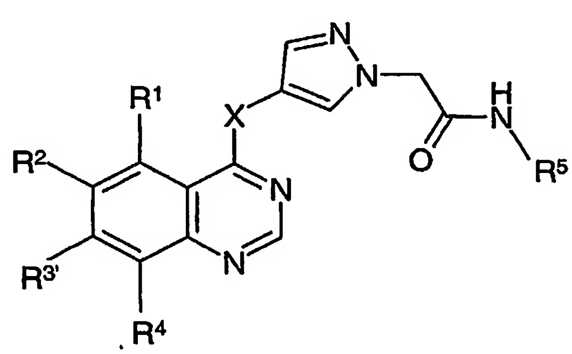
R^{14} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl;

R^5 is aryl or heteroaryl optionally substituted by 1, 2 or 3 substituents independently selected from halo, hydroxy, cyano, nitro, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, CONHR^{17}, NHCOR^{18} and S(O)$_p$R^{19} where p is 0, 1 or 2;

R^9, R^{10}, R^{15} and **R^{16}** are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl and di(C_{1-6}alkyl)aminoC_{1-6}alkyl;

R^{17}, R^{18} and **R^{19}** are independently selected from hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{2-4}alkenyl and C_{2-4}alkynyl.

2. A compound of formula (IA)



formula (IA)

where X, R^1, R^2, R^4 and R^5 are as defined in relation to formula (I) in claim 1 and $R^{3'}$ is hydrogen, halo or $-X^{3'}R^{13'}$;

$X^{3'}$ is a direct bond, $-CH_2=CH_2-$, -O-, -NH- or $-N(C_{1-6}alkyl)-$;

$R^{13'}$ is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkenyl where the group is substituted by $-NR^{7'}R^{8'}$;

$R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, heterocyclyl, C_{1-6}alkyl, phosphonooxyC_{1-6}alkyl, C_{1-3}alkoxyC_{1-6}alkyl, phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-3}alkyl, phosphonooxyC_{3-6}cycloalkyl, phosphonooxyC_{1-4}alkylC_{3-6}cycloalkyl, phosphonooxyC_{3-6}cycloalkylC_{1-3}alkyl, C_{1-3}alkoxyC_{3-6}cycloalkyl, C_{1-3}alkoxyC_{3-6}cycloalkylC_{1-3}alkyl, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{3-6}cycloalkylC_{1-3}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, cyanoC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-3}alkylaminoC_{1-6}alkyl and di(C_{1-3}alkyl)aminoC_{1-6}alkyl; provided that at least one of $R^{7'}$ and $R^{8'}$ contains a phosphonooxy substituent;

or $R^{7'}$ and $R^{8'}$ together with the nitrogen to which they are attached form a heterocyclic ring which ring comprises 4 to 7 ring atoms of which one is nitrogen and of which another is optionally selected from N, NH, O, S, SO and SO_2, and which ring is substituted on carbon or nitrogen by 1 or 2 groups independently selected from phosphonooxy, phoshonooxyC_{1-4}alkyl and phosphonooxyC_{1-4}alkoxyC_{1-4}alkyl, and where a ring $-CH_2-$ is optionally replaced with a $-C(O)-$.

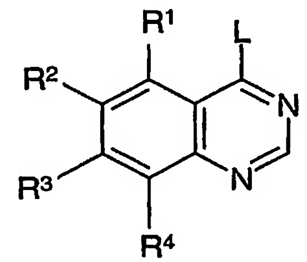
3. A compound according to claim 1 or claim 2 for use as a medicament.

4. The use of a compound according to claim 1 or claim 2, in the preparation of a medicament for the treatment of a disease where the inhibition of one or more Aurora kinase(s) is beneficial.

5. The use according to claim 4 where one or more Aurora kinase(s) are Aurora-A kinase and/or Aurora-B kinase.

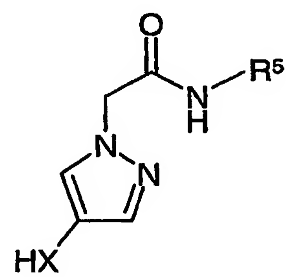
6. A pharmaceutical composition comprising a compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt, ester or prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

7. A process for the preparation of a compound according to claim 1 or a pharmaceutically acceptable salt, ester or prodrug thereof, which process comprises reacting a compound of formula (II)



(II)

where L is a suitable leaving group such as chloro, bromo, SMe with a compound of formula (III)



(III)

in the presence of hydrochloric acid in dioxane under an inert atmosphere, and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt, ester or prodrug thereof.

8. A process for the preparation of a compound according to claim 2 or a pharmaceutically acceptable salt thereof, which process comprises phosphorylation of a compound according to claim 1, followed by deprotection of the phosphate group to yield a compound according to claim 2.

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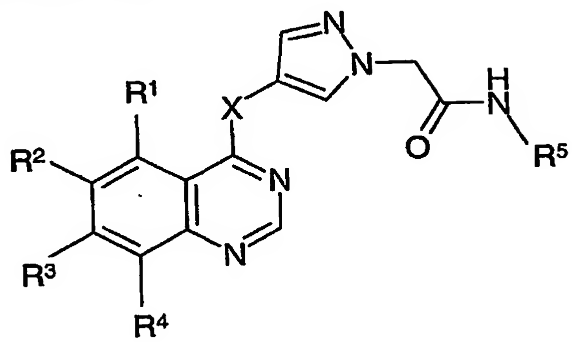
ABSTRACT

TITLE: **CHEMICAL COMPOUNDS**

Quinazoline derivatives of formula (I)



formula (I)

for use in the treatment of proliferative diseases such as cancer and in the preparation of medicaments for use in the treatment of proliferative diseases, and to processes for their preparation, as well as pharmaceutical compositions containing them as active ingredient.

PCT/GB2004/001614